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MUSCULAR RIGIDITY WITH AND WITHOUT SYMPATHETIC INNERVATION *

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The old question of the influence of sympathetic nerve fibers on the so-called tonus of skeletal muscle has recently attracted renewed attention, in view of a somewhat widespread agitation for surgical relief of spastic paralysis by "ramisection." A great deal of experimental work has been directed to this problem, and a still larger amount of speculation has been expended on it. Yet the problem seems to be still in a decidedly unsettled state.

So much of the previous work has been inconclusive and so conflicting has been the testimony that we have attempted to clarify the subject by emphasizing quantitative methods of experimentation, by searching carefully for all possible sources of experimental error, and by critically examining our results and the various arguments in the light of modern knowledge of nerve-muscle physiology. Perhaps the chief justification for adding to the already heavily burdened literature of the subject is the uncertainty in the minds of many surgeons as to whether or not the operation of ramisection is advisable for their patients.

The literature of the subject has recently been admirably reviewed by Cobb.[1] The salient points may here be summarized. The basis of the argument for this operation to relieve spastic paralysis seems to be, in the first place, the anatomic observation by Boeke [2] apparently showing that skeletal muscle fibers are innervated by sympathetic as well as by cerebrospinal nerve fibers. This observation naturally led to a search

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1. Cobb, S.: Physiol. Rev. **5**:518 (Oct.) 1925.

2. Boeke, J.: Internat. Monatschr. f. Anat. u. Physiol. **28**:377, 1911. Boeke, J., and Dusser de Barenne, J. G.: Proc. Sect. Sc. Wet. Amsterdam **21**:1227, 1919.

for the functional significance of the sympathetic fibers, and, on cutting these in frogs, De Boer [3] found a loss of "tone." On the strength of these observations Langelaan [4] built a theory that "contractile tonus" (by which the limb assumes a posture) depends on the cerebrospinal nerve fibers, and "plastic tonus" (by which the limb maintains a posture already assumed) depends on the sympathetic fibers. He performed experiments purporting to differentiate between plasticity and contractility as muscular functions. In support of his views he cited Sherrington's observation [5] on "plastic tonus," i. e., the "lengthening" and "shortening" reactions whereby in the decerebrate mammal the limb, when passively extended or flexed, tends to remain in the posture imposed. More recently Hunter,[6] assuming Langelaan's theory to be valid, performed experiments in which he claimed to have shown that cutting the sympathetic fibers destroys the plastic element in tonus, leaving the contractile element unimpaired. On the strength of these observations Royle [7] undertook to introduce the operation of ramisection with the idea that, by removing the plastic element in tonus, relief of the condition of spastic paralysis would be effected. Coombs and Tulgan [8] and also Kuntz and Kerper [9] have recently reported a few observations on cats tending to support Hunter's view.

Both Cobb [10] and Dusser de Barenne,[11] seeking to test the question by critical experiment, were unable to find any influence of sympathetic nerves on tonus in skeletal muscles, decerebrate or otherwise. Several other investigators, notably Kanavel, Pollock and Davis,[12] have likewise failed to substantiate De Boer's results. Since the completion of our experiments, a report has appeared of a similar series on dogs by Meek and Crawford,[13] corroborating the work of Cobb in showing the absence of any demonstrable influence of sympathetic nerves on tonus in the limb muscles. Therefore, the bulk of experimental evidence

3. De Boer, S.: Ztschr. f. Biol. **65**:239, 1915.

4. Langelaan, J. W.: Brain **38**:235, 1915.

5. Sherrington, C. S.: Quart. J. Exper. Physiol. **2**:109, 1909.

6. Hunter, J. I.: Surg. Gynec. Obst. **39**:721 (Dec.) 1924; Am. J. M. Sc. **170**:469 (Oct.) 1925.

7. Royle, N. D.: Surg. Gynec. Obst. **39**:701 (Dec.) 1924.

8. Coombs, H. C., and Tulgan, J.: Am. J. Physiol. **74**:314 (Oct.) 1925.

9. Kuntz, A., and Kerper, A. H.: Proc. Soc. Exper. Biol. & Med. **23**:77, 1925.

10. Cobb, S.: Am. J. Physiol. **46**:478 (July) 1918.

11. Dusser de Barenne, J. G.: Folia neuro-biol. **7**:651, 1913.

12. Kanavel, A. B.; Pollock, L. J., and Davis, L. E.: Experimental and Clinical Experiences with Sympathectomy in Spastic Paralysis, J. A. M. A. **83**:1615 (Nov. 15) 1924.

13. Meek, W. J., and Crawford, A. S.: Am. J. Physiol. **74**:285 (Oct.) 1925.

seems to be against the view that sympathetic nerve fibers contribute directly to tonus in skeletal muscle.

Hunter [14] made answer to the negative findings of Cobb and Dusser de Barenne by emphasizing the distinction made by Langelaan between plastic and contractile tonus. He assigned to the coarser muscle fibers, innervated by cerebrospinal nerve fibers, the function of contraction; and to the more slender fibers, innervated, according to Kulchitsky,[15] by sympathetic nerve fibers, a function similar to that of the molluscan "catch" muscle; viz., the ability to maintain posture already imposed either passively or by contraction of the coarser fibers (comparison should be made with observations of Needham [16]). He ascribed the negative results of other workers to the failure to recognize the presence or absence of *"plastic"* tonus, for he contended that this and only this element is abolished by cutting the sympathetic fibers. Decerebrate rigidity, he said, will still be present, for it depends, in part, on the contractile function. The experiment must be especially designed to show the presence of the plastic element in tonus; lengthening and shortening reactions and the ability to maintain posture against the force of gravity should be especially noted as evidence to show whether or not the plastic function has been disturbed.

Cobb has shown in his review [1] that Langelaan's theory is without real foundation, in that no crucial evidence has been brought forward to prove the existence of any two such elements in tonus as he assumes. It should be noticed that Sherrington never maintained that plasticity was a separate function from contractility in tonus. He merely called attention to the superficial similarity between the plastic decerebrate limb and the adductor apparatus of the mollusk, in the ability of the muscle in each case to maintain a given degree of shortening irrespective of the amount of tension. He also furnished evidence tending to show that this behavior was due to proprioceptive reflexes; i. e., reflexes initiated by afferent impulses arising within the muscle involved. But he made no assumption as to the type of motor-nerve fibers or of muscle fibers involved, merely noting the striking degree of plasticity conferred on the limb by its proprioceptive reflexes.

Two considerations derived from our experience throw doubt on the existence of these alleged functionally distinct elements in tonus, the plastic and the contractile, and especially on the view that they are relegated to distinct neuromuscular mechanisms.

1. In observing more than 200 decerebrate cats, in the course of a variety of researches on spinal reflexes, we have seen all grades of

14. Hunter (footnote 6, second reference).

15. Kulchitsky, N.: J. Anat. **58**:152, 1924.

16. Needham, D. M.: Physiol. Rev. **6**:1, 1926.

decerebrate rigidity from extreme extension strongly maintained, on the one hand, to complete flaccidity, on the other. When rigidity is extreme it is difficult to force passive flexion, and the tendency to return to full extension is so great that it is difficult to obtain the lengthening reaction. When the rigidity is weak there is not enough tonic activity to show the plastic effects to advantage. Therefore, these reactions of plastic tonus are best revealed in the intermediate state of moderate rigidity. We have seen nothing that suggests any other determining condition for plasticity than a moderate degree of decerebrate rigidity. The plastic reactions seem to be more simply explained, as suggested by Sherrington, through the operation of proprioceptive (myotatic) reflexes, the end organ being the contractile muscle innervated by cerebrospinal nerve fibers, than by invoking a special plastic mechanism in the muscle. Indeed, since decerebrate rigidity is marked by action currents indistinguishable in form and rhythm from those in other sustained contractions, we see no reason to suppose that tonus in skeletal muscle involves any function fundamentally different from any other contraction.

2. It is difficult to reconcile the alleged plastic function of the sympathetic nerves with the known facts of nerve-muscle physiology. Before nerve physiology had reached its present state it was customary to think of the nerve trunk as if it were a wire carrying an electric current, or a pipe conducting a stream of fluid, and to treat stimulation as if it set up a steady stream of energy which could be graded in amount or intensity without limitation. We now know that the stream of nervous energy, however initiated, consists in individual nerve impulses, each impulse in a single nerve fiber being a brief, transient event, of explosive character, in that it exhausts all the energy available at the moment, and therefore obeys the all-or-nothing law. Thus, instead of a steady stream of nervous energy, we have a sequence of separate impulses whose frequency is limited by the refractory period of the conducting fiber.[17] Now Langelaan's theory, on which Hunter and Royle base their work, holds that plastic tonus is controlled by the sympathetic nerve fibers, which implies that motor impulses in these fibers initiate this function in the muscle fibers. Indeed, we know of no influence conveyed by nerves, other than nerve impulses, which could evoke any sort of functional response in muscle. All experimental evidence points to the view that the functional response in a given excitable tissue, nerve or muscle, is of one kind; i. e., no qualitative differences are possible in the nerve impulse, nor in the corresponding response of a given muscle fiber. The quantitative differences in the activity of a given tissue depend solely on the number of functional

17. Lucas, K.: The Conduction of the Nervous Impulse, London, 1917.

units (fibers) excited and on the number of individual responses evoked in each fiber in a given time, and, in the case of muscle, on the load encountered.[18] Furthermore, the properties of all skeletal muscles seem to be such that functional response always results in contractile effort. The quickness and strength of contraction may differ enormously in different types of muscle, but all are alike in their tendency to contract on excitation, and excitation of skeletal muscle by the nerve impulse evokes the same type of response as direct artificial excitation. Therefore, all the evidence now known fails to show how sympathetic nerve fibers could convey messages to skeletal muscle fibers, telling them to hold their length unchanged, without releasing contractile energy in them.

It is true that the molluscan adductor muscle, which has served in the literature [19] as the prototype of plastic tonus, presents a behavior apparently as difficult to explain in terms of individual functional response as the alleged plasticity in mammalian skeletal muscles. The "catch" muscle has not been found to play a measurable part in effecting motion, yet it has enormous power to maintain posture against great tension. And the exercise of this function is dependent on the innervation of that muscle. The phenomenon is baffling, yet conceivably experimentation, sufficiently refined, would reveal even in the "catch" muscle a release of contractile energy in response to each volley of impulses set up in the appropriate motor nerve. The difference between the "catch" muscle and the contractile muscle might be found to lie in a far more sluggish and far less fatigable response in the former than in the latter, and yet the fundamental nature of the response might be the same in both. Similarly, we might find that the slender muscle fibers innervated by sympathetic nerve fibers in mammalian skeletal muscles, respond to excitation by nerve impulses with measurable contractile effort, but differ from the coarser fibers in the sluggishness of their contraction. If this were the case, and if the slender fibers participated in the general proprioceptive reflexes which Sherrington has demonstrated in the decerebrate mammal, then they would contribute relatively more than the coarse fibers to the plastic or postural property of these reflexes, for the greater duration of each contractile response would serve for adaptation to the sustained effort of maintaining posture. But experiments in which the sympathetic nerves are stimulated should reveal a contractile effort, if this were of sufficient magnitude to play an important rôle in the

18. It is conceivable that some special structure, e. g., the neurofibrils, constitute a conducting path, distinct from the rest of the nerve fiber, and that this evokes a response in a corresponding distinct mechanism, e. g., the sarcoplasm, in the muscle; no evidence exists in support of this view, and it is at best pure speculation. Cobb (footnote 1, p. 528).

19. Bayliss, W. M.: Principles of General Physiology, London, 1924, p. 536.

mechanical activity of the muscle; yet all such experiments have failed to show any measurable contraction.[20] The slender fibers differ less, histologically, from the coarse fibers in mammalian muscle than do the fibers of the "catch" muscle from those of the contractile muscle in the mollusk; therefore, though in the mollusk we might expect to find so sluggish a contraction in the "catch" muscle that it would be difficult to record, we should hardly expect this difficulty to be insuperable in the case of the slender fibers of the mammalian muscle.

In spite of these objections to the theory that the sympathetic nerves control a plastic element in the tonus of skeletal muscles, and in spite of the preponderance of experimental evidence against the existence of any direct influence of these nerves on skeletal muscle, the fact that Hunter and Royle appear to have shown such an effect in certain animals renders it fitting that a careful examination should be made with reliable quantitative methods. For it may be that although decerebrate rigidity is almost as great after the sympathetic nerves have been cut as before, there is still a slight difference which careful experimentation would reveal. If so, it should be revealed consistently in a large series of animals.

There is one important fallacy in the argument of Hunter and Royle which must be noted. They contend that plastic tonus is maintained by sympathetic nerve fibers, yet they also say that the effect of sectioning these nerves becomes greater for days and even weeks after it is done. Now it has been shown, with a string galvanometer and an electron-tube amplifier connected with a skeletal muscle, that rapid section of the motor nerve evokes functional responses in the muscle for about a minute, after which the muscle becomes wholly inactive;[21] in other words, the freshly cut surface of the nerve continues to be a source of excitation and to initiate nerve impulses for this length of time and no more. The foregoing is probably the most sensitive known method of detecting functional responses in muscle. It is improbable that nonmedullated nerve fibers differ from medullated fibers profoundly in this respect, and it is safe to conclude that within a few minutes after section, all impulses have ceased to flow to the denervated muscle. Therefore, whatever change in behavior results from stopping the stream of nerve impulses to these muscle fibers, it should be fully established a few minutes after the operation. Further changes, requiring days or weeks to develop, cannot be due to the simple cessation of motor-nerve impulses. If these changes develop they must be due to some secondary cause, such as a shift in circulation or a modification in the physical state of the fibers from disuse. In looking for effects of

20. Cobb (footnote 10). Wastl, H.: J. Physiol. **60**:109 (July) 1925.

21. Forbes, A., and Cattell, M.: Am. J. Physiol. **70**:140 (Sept.) 1924.

removal of the sympathetic nerve supply, we should therefore seek in the *immediate* result of the operation evidence as to the direct dependence of mechanical effects on sympathetic nerve impulses; and we should also follow the delayed effects of the operation in an effort to see whether indirect or secondary changes could be found corresponding to those described by Hunter and Royle.

These authors maintained that the effects they described appeared better in the goat than in the cat. Their conclusions were based on the most favorable six out of nine or ten experiments on goats, and it seems to us that a much larger series of animals is required to justify conclusions. Aside from the fact that it was not feasible to obtain and handle goats in large enough numbers for an adequate series, we felt that, if there were indeed a physiologic phenomenon of significance for mammals in general and therefore having a bearing on human surgery, it should be possible to demonstrate it in the cat. Furthermore, extensive experience with decerebrate cats over many years furnished a background for comparison, which was lacking in the case of the goat. We have, therefore, used cats in our experiments.

METHOD

In twenty-five cats the sympathetic innervation of either a fore limb or a hind limb was surgically destroyed. Of the twenty-five animals, seventeen were successfully decerebrated and the subsequent condition of all four limbs was carefully examined. Since, for the reasons already given, the loss of any true functional response in a muscle should immediately be apparent, cutting the sympathetic nerves after decerebration should serve to reveal the alleged function, if it really exists. We therefore performed three experiments in which the animal was decerebrated first. The degree of decerebrate rigidity was noted in all four limbs, then the sympathetic innervation of one of them was destroyed and the result of this destruction sought at once. But since the observations of Hunter and Royle suggested the possibility of some delayed secondary effect of interrupting the sympathetic nerve supply, it seemed best to follow their procedure in the majority of our experiments; that is, to do a preliminary aseptic operation in which the sympathetic innervation was destroyed and then, after a suitable interval, to decerebrate the animal and compare the limb in question with the others. Of the seventeen successful experiments, six dealt with the hind limb and eleven with the fore limb. The fore limb seemed preferable for the reason that the entire sympathetic nerve supply of one limb can be destroyed by the rapid operation of removing the stellate ganglion, an operation that has been employed in this laboratory in connection with other researches.[22] This operation requires only about fifteen minutes in

22. Cannon, W. B.; Lewis, J. T., and Britton, S. W.: To be published.

the hands of a practiced operator and involves no possibility of disturbing the sympathetic supply of the opposite foreleg. The operation for interrupting the sympathetic innervation of the hind leg involves extirpation of the abdominal sympathetic chain for several segments and is a much more severe and difficult operation. It was done, however, in six cases in order that a certain number of our experiments should duplicate as nearly as possible the procedure of Hunter and Royle.

Experiments of this sort are teeming with possible sources of error, and we therefore devoted particular attention to the appraisal and elimination of these as far as possible. Experience with a great many decerebrate cats has shown us that there are frequently differences in decerebrate rigidity between the two sides of an animal. One possible cause of this might be asymmetrical transection of the brain-stem in decerebrating. With this in mind, we took pains to make the transection as symmetrical as possible.

The influence of the position of the animal as a whole, and in particular of the neck muscles, has been shown by Magnus and De Kleijn [23] to be great in determining the distribution of decerebrate tonus among the muscles of the various limbs. In previous researches, our experience has shown that when a decerebrate animal is left lying on one side, the limbs of the side on which it lies usually exhibit greater rigidity than the opposite limbs. This may be due to some such influence as Magnus has traced to the neck muscles, or it may conceivably result from unequal distribution of the blood supply in the brain-stem or spinal cord, due to the force of gravity. In our experiments, therefore, we took pains to maintain the animal in as perfectly symmetrical a position as possible from the time of decerebration throughout the experiment. This was usually done by placing the animal astride a holder which supported the trunk and allowed the limbs to hang down vertically on the two sides. In order to determine the amount of error that might result from a slight lack of symmetry in position, and also any influence of neck posture, we made a point of rotating the head and neck in various planes —both to right and left—and noted the degree of rigidity in all four limbs with the head held in many different positions.

Another possible source of error to be guarded against is that due to the effect of manipulation of the limbs under observation. The lengthening reaction, described by Sherrington, consists in the relaxation of the extensor muscles when the limb is passively flexed, and appears to result from a reflex inhibition due to proprioceptive impulses. In feeling the resistance of the limb to passive flexion one is apt to induce the lengthening reaction to a greater extent in the limb on which the

23. Magnus, R., and De Kleijn, A.: Pflüger's Arch. f. d. ges. Physiol. **145**: 455, 1912.

attention is focused than in the opposite limb with which it is being compared; in this way one gets a false impression of diminished tonus. We therefore handled the two opposite limbs simultaneously and as symmetrically as possible. This point is important and will be referred to again later.

As already stated, our experiments were divided into two groups, those dealing with the fore limb, and those with the hind limb. In removing the stellate ganglion for interruption of the sympathetic fibers supplying the fore limb, the chest was opened. Artificial respiration was therefore necessary. This was arranged, after the animal had been deeply etherized, by passing a rubber catheter 3 mm. in diameter through a mouth gag into the trachea to a point a short distance above the bronchial bifurcation. Respiration was continued by an interrupted blast of air which passed through an ether bottle so arranged that the degree of etherization could be nicely regulated. Then the skin over the first intercostal space on the left side was surgically cleaned, all necessary aseptic precautions being taken. The thorax was opened through an incision along the first intercostal space. The first and second ribs were pushed apart by means of a rib spreader, and as the spreader widened the gap, the intercostal muscles were cut further until a satisfactory view of the top of the chest cavity was obtained. By means of a blunt dissector, the stellate ganglion was sought deep in the depression at the back of the thorax. When found, the ganglion was grasped in mouse-tooth forceps, was gently lifted, and, after being separated by means of scissors from all its connections, was completely removed. The first and second ribs are so close that it is unnecessary to draw them together by sutures. After the ganglion had been removed and a slightly increased air pressure had inflated the lung, so that it filled the chest, the different muscle layers were sewed together, and the wound was closed.

Destruction of the sympathetic innervation of the hind limb was performed as follows: Under deep anesthesia, a long incision was made on the side of the abdomen and the muscles were divided until the peritoneum was revealed. The peritoneum was reflected inward and the dissection carried down until the aorta and the vena cava were brought to view. These vessels were then drawn to one side and the two sympathetic trunks were revealed lying on the ventral surface of the spinal column. The sympathetic chain on the desired side was then removed from about the level of the fifth lumbar vertebra to a point well within the pelvis, just above the junction of the two chains. In this way the last three ganglions above the junction were removed; this destroyed the sympathetic innervation of the gastrocnemius and soleus muscles, whose tonus was especially studied. Part of the sympathetic

supply of the knee extensors also was involved in this operation. Great care was exercised to avoid injuring the opposite sympathetic chain.

Decerebration was regularly performed under deep ether anesthesia, with the Sherrington guillotine.[24] The carotid arteries were first ligated, and then, while an assistant compressed the vertebral arteries to restrain hemorrhage, a large chisel was driven through the cranium, guided by certain landmarks, in such a way that the transection of the brain-stem occurred at about the level of the anterior colliculi. Usually the first transection with the chisel was practically symmetrical and at approximately the desired level, but to make sure of this point, the brain-stem was quickly examined and any slight lack of symmetry found was corrected with a sharp knife. The symmetry of transection usually was further verified at necropsy. Pressure was continued on the vertebral arteries until clotting stopped further hemorrhage. As soon as the transection was made, the animal was placed astride the holder already mentioned, in order to maintain a strictly symmetrical posture.

Methods of Observation.—In animals sympathectomized before decerebration (constituting all but three of our series) the general condition was watched, and though no measurements were made, observation would reveal any marked lack of symmetry of action. After decerebration, the rigidity was tested manually by placing one hand under each foot and lifting simultaneously. As already mentioned, more decerebrate rigidity is sometimes found on one side than on the other in both fore and hind legs, irrespective of any sympathetic operation. In any given experiment the sympathetic operation involved only one leg, leaving one pair unaffected for use as control. In order to avoid interpreting an inherent difference as evidence of an operative change, we not only compared the operated limb with its mate, but also made a similar comparison between the two limbs of the unaffected pair. For example, when the stellate ganglion was removed we not only tested the fore limbs but the hind limbs as well.

This crude manual method of comparison served very well to reveal any real and consistent differences in rigidity between the two sides; but to render our observations as strictly quantitative as possible, we made use of spring balances. Two somewhat different ends were sought in these measurements: (*a*) to compare the rigidity in the two legs at the same moment, by a method which should reveal inequalities as surely and accurately as possible, and (*b*) to obtain an absolute measure (even if only approximate) whereby we could assign a value to the rigidity, making it comparable in a given limb from hour to hour and even in

24. Sherrington, C. S., and Miller, F. R.: Quart. J. Exper. Physiol. **9**:147, 1915.

corresponding limbs of different animals. The method which proved most satisfactory for the first purpose was to tie spring balances by means of threads to symmetrical points near the feet on the two limbs to be compared, and to pull with both balances in a parallel direction such that the pull tended to flex both limbs. Sometimes we compared the resulting flexion on the two sides, under equal tension, but we found it more satisfactory to pull with tension sufficing to produce symmetry in the position of the two legs, i. e., equal flexion, and then measure the requisite tension on each side. The latter procedure was adopted as our standard method, and was repeated with two or three different degrees of flexion in each comparison.

This method was the most satisfactory for determining whether or not the rigidity was the same or different in a pair of limbs, and by supporting the animal above the table by trunk and hip, to enable the thread to pass the flank without friction, it could be applied fairly well even when the animal lay on one side. But to provide a more absolute measure of rigidity the correlation of angle of flexion with tension was desirable. In order to measure muscle tension in the fore limbs in this way we placed the animal astride the support, tied a string around the elbow on one side, led it round the rear end of the support and tied it to the elbow on the other side. This string was tied tight enough to prevent forward motion of the shoulder joints. A string was then tied to each fore limb at the wrist, care being taken to apply them at exactly symmetrical points, and the hooks of the spring balances were inserted into loops at the ends of these strings. A steady pull with each spring balance at various tensions, perpendicular to the line of the radius, was maintained, and the resulting angles between this bone and the humerus on each side were measured. To facilitate this, we first measured the angle between the humerus and the horizontal string which passed around the back of the support. Since the string held the humerus in a fixed position this angle served as a convenient constant. Thereafter, in the individual measurements, the angle between the radius and the horizontal string was recorded (fig. 1). This was done by holding the straight edge of a celluloid protractor in line with the radius, and reading off the angle thus made with the horizontal string. It was much easier to make accurate measurements in this way than by attempting to measure the angle between the radius and the humerus directly.

In observations on the hind limb the ankle was used as the test joint. Sutures of white thread were passed through the skin, marking the position of the femur from hip to knee and of the tibia from knee to ankle. The knee joint was so held by an assistant that these threads made a right angle, and the two feet were pulled by spring balances tied to them with threads. The bony prominences were used as land-

marks to insure symmetrical application, and the pull was exerted perpendicularly to the metatarsal bones. The angles which these made with the tibia were recorded by means of the celluloid protractor. In this way the decerebrate tonus of the gastrocnemius muscle was measured. The precaution of holding the hip and knee fixed is important, since the position of these joints is a factor in determining the tension on the gastrocnemius muscle. Great pains were taken, therefore, to hold the hip and knee joint rigidly in as symmetrical a position as possible, while the tonus of the gastrocnemius was being measured in this way. This method could be used either with the animal astride the support or lying on one side.

When the animal was astride the support we were able to combine the absolute and relative measures. In the case of both fore limbs and

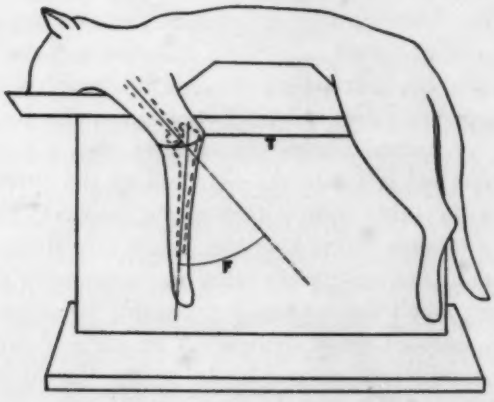

Fig. 1.—Cat astride holder, showing method of measuring angle of elbow flexion: *T*, thread passing from elbow around the rear end of holder *F*, angle of flexion, used in figure 2 and table.

hind limbs we sometimes exerted the same pull on the two sides and measured the angles. In other cases, we pulled the joints to the same angle and compared the tension on the two sides. In making these observations we paid attention to the degree of accuracy attainable and the resulting dependability of the measurements. To this end we often repeated the measurements several times in each case.

In some experiments, electromyograms were made from extensor muscles. This was usually done in the case of the gastrocnemius muscle. Small windows were cut in the skin, one over the middle, the other over the tendinous end of the muscle, and agar electrodes, previously described,[25] were applied with sutures through the fascia. These were

25. Forbes, A., and Olmsted, J. M. D.: Am. J. Physiol. **73**:25 (June) 1925.

connected with a Hindle string galvanometer. Records were then taken while the limb was undisturbed; that is, such action currents were registered as were due to decerebrate rigidity alone. Then, with the femur and tibia held rigidly, the gastrocnemius was subjected to a passive stretch by pulling with a spring balance on the thread tied to the feet. The electromyogram of the resulting myotatic reflex was recorded, and, at the same time, the amount of tension applied with the spring balance was noted. The procedure was applied both on the side whose sympathetic innervation was destroyed and on the intact side. If a marked loss of tonus had resulted from cutting the sympathetic nerves, and the mechanism involved was not characterized by the usual action currents of skeletal muscle, the mechanical difference between the two sides should appear without a corresponding difference between the electromyograms.

Necropsies were performed on several of the animals to be sure that the sympathetic supply of the limb had indeed been destroyed. In the case of the fore-limb experiments, in which the stellate ganglion was removed, this precaution was really unnecessary, since the abnormal position of the nictitating membrane regularly furnished evidence that the stellate ganglion had been successfully removed, but in a few instances the postmortem examination was made to eliminate all possibility of doubt.

RESULTS

In recording our results it may be well to begin with the preliminary observations made by one of us in connection with another research, in which both stellate ganglions were removed from a series of nineteen cats. Of these animals, fifteen, when decerebrated within an hour after removal of the ganglions, showed marked extensor rigidity in the fore limbs. As the entire sympathetic innervation of the fore limbs was destroyed, these observations clearly prove that decerebrate rigidity does not depend for its existence on sympathetic motor-nerve impulses. But since this point has already been established by previous work, and the advocates of the sympathetic nerve doctrine now contend that it is the *plastic* element in tonus that depends on these nerves, we must seek for evidence of quantitative or qualitative change in tonus traceable to the loss of sympathetic innervation.

In the first three experiments of our series, those in which decerebration was done first, we noted especially the amount of variation in the rigidity of the individual limbs before operating on the sympathetic nerves. In doing this we tried to ascertain the amount of change that could be traced to the controllable conditions of the experiment, and the amount of variation that might occur even under the most carefully controlled conditions.

Our first experiment was especially favorable for this purpose, since after decerebration (before the sympathetic operation) the cat, when held in a symmetrical posture, showed symmetrical rigidity, as nearly as we could judge by palpation. When the cat was laid on the left side, the rigidity at once became slightly but distinctly greater in the left hind leg than in the right. When placed on the right side, the rigidity was much greater in the right hind leg than in the left. The position was again reversed and again the rigidity became slightly greater in the left leg. Applying the spring balances simultaneously, with pulls sufficing to produce symmetry in the position of the two legs, the tension on each side was measured; this was repeated with two or three different degrees of flexion. The measurements clearly corroborated the findings on palpation, showing the leg on which the animal lay to be the more rigid of the two. For instance, with the cat on the right side, when the rigidity was felt to be much greater in the right leg, the tension required for symmetry was as follows: right, 200 Gm.; left, 90 Gm.; at greater flexion, right, 250 Gm.; left, 110 Gm. When we pulled with equal tension on the two sides, the displacement of the legs, measured in centimeters, harmonized with the foregoing measurements, the more rigid leg showing the less displacement.

To test the source of error arising from the proprioceptive effects described by Magnus and De Kleijn, we rotated the head in this animal and found changes in rigidity, which could be recorded quantitatively by correlation of angle with tension. Raising the head, as the cat lay on one side, caused a measurable loss of rigidity in the uppermost hind leg, the average difference at equal tensions being about 14 degrees of flexion.

After a series of observations of this sort, lasting about two hours from the time of decerebration, the abdominal sympathetic chain was laid bare. Then for another forty minutes similar observations were made, to make sure there was still no marked difference in rigidity between the two hind legs. Then the left sympathetic chain was removed from the crus of the diaphragm approximately to the pelvic brim, thus eliminating all but the last ganglion involved in the innervation of the leg muscles. For a few seconds after this procedure no rigidity could be felt in the left leg. Within a minute it had returned and was for a time greater, by the spring-balance test, than just before removal of the ganglions. More fluctuations followed, but no marked, consistent difference between the two sides. If there was any real diminution of rigidity in the sympathectomized leg, it was too slight to be distinguished from the usual spontaneous fluctuations.

The second animal in which decerebration preceded sympathectomy was also favorable for the desired comparisons. After decerebration the

rigidity was symmetrical in the two sides, as far as palpation could determine, whether the animal was astride the support or lying on one side. A comparative test of angles in the ankle joint with the spring balance, made first on the left leg with the animal on the right side, and then in the reverse arrangement, showed a strikingly close agreement between the two sides. Raising the head caused slight loss of rigidity in the uppermost limb, as in the previous animal. There was some convulsive activity and there were fluctuations of rigidity before the sympathetic operation, which was performed an hour and a half after decerebration. The left abdominal sympathetic chain was removed well into the pelvis. Immediately after the operation there was no rigidity in any of the limbs. In three minutes it returned, and during the next seven minutes both simultaneous palpation and successive spring-balance measurements (the animal first on one side, then the other) clearly and consistently showed *less* tonus on the operated side. This observation would appear to support the findings of Hunter and Royle, but for the fact that at the same time we noted distinctly less rigidity in the left *fore* limb, as well as the hind, although neither fore limb was involved in the operation. We then removed the *right* abdominal sympathetic chain, after which the left hind leg continued consistently to show less rigidity than the right. At this time good myotatic reflexes were shown by electromyograms on the right side, but none on the left. It was also noted that the lengthening and shortening reactions of Sherrington (plastic tonus) were present in the right leg after its sympathetic innervation was removed. Thus this animal proved in the end to afford no support to the theory of sympathetic plasticity, but rather to show how deceptive an experiment of this sort may be, in consequence of uncontrolled changes.

The third animal decerebrated before sympathectomy also showed symmetrical rigidity when placed astride the support, both in the fore and hind limbs. Ten minutes after decerebration the left stellate ganglion was removed. Four minutes after this operation the rigidity was marked in both fore legs, the cat lying on its back. Two observers thought there was a little less rigidity on the operated side; a third observer was unable to detect any real difference by palpation. Five minutes later, with the animal astride the support, no difference at all could be felt between the two sides. When four minutes had elapsed a careful simultaneous test with spring balances showed complete symmetry of rigidity in the fore legs. Angles of elbow flexion correlated with tension, in a long series of tests, showed almost perfect symmetry in the forelegs for the next half hour. There were fluctuations from moment to moment, but when the tests were simultaneous, the hind legs also showed symmetry within the limits of observational error. The

lengthening and shortening reactions of plastic tonus were elicited in both hind legs. In the fore limbs, in which rigidity was greater, it was possible to obtain an imperfect lengthening reaction; that is, the elbow yielded slightly to forced flexion, but release of the foot was followed by full extension. No difference in this respect was found in the two sides. For four hours after excision of the ganglion, no difference could be felt between the two sides. Five and a half hours after operation a slight but definite difference was noted, the operated side showing a little less rigidity. Three hours later there was no perceptible difference, but eleven and a half hours after excision of the ganglion the difference was again definite. No further observations were made.

These three experiments serve to show that fairly wide variations in decerebrate rigidity may result from placing a cat in an unsymmetrical posture. They also show that when the animal is carefully maintained in a perfectly symmetrical posture, rigidity is usually symmetrical, that is, equal in the two limbs of a pair, and thus affords a fair basis for testing the effect of the sympathetic operation. But this symmetry cannot be regularly relied on, for uncontrollable fluctuations occasionally occur in a way that may confuse the effects of an operation.

As to the effect of destroying the sympathetic innervation in these experiments, we should note that in both abdominal operations there was an immediate loss of rigidity, in one case involving all the limbs. This may well have been due to the reflex inhibition of rigidity by the powerful sensory stimulation involved in the operation. If so this phenomenon has no bearing on the problem of sympathetic innervation. The observations made after the requisite time had elapsed for such sensory stimulation to cease showed no definite and consistent effect on rigidity resulting from the operation. The third animal (stellate) showed the most persistent lessening of tonus on the side operated on, but even in this case it was intermittent, with interspersed periods of symmetry, and the difference was too slight to warrant any conclusions.

As was stated in the section on method, in all of our experiments except the three just described, the removal of sympathetic innervation, stellate or abdominal, was performed aseptically first, and then after an interval varying from three to eighty days the animal was decerebrated. In practically all these experiments repeated observations were made with a spring balance, by the methods described above, affording, as far as possible, both the immediate, simultaneous comparison in a given pair of limbs and the more absolute, if rougher, measure wherein the angle of flexion was correlated with tension. A few typical curves illustrating the latter correlation are given for individual experiments. Each curve is made up of measurements taken in rapid succession to avoid confusion due to progressive or fortuitous changes of rigidity. In some cases two

measurements of angle were made at each tension and the measurements averaged. In all cases shown in these curves the animal was astride the holder and both limbs of the pair under observation were pulled symmetrically, the readings being made first from one, then the other. Figure 2 shows four pairs of curves from the fore limbs in the case of three stellate experiments. The method of plotting used by Kuntz and

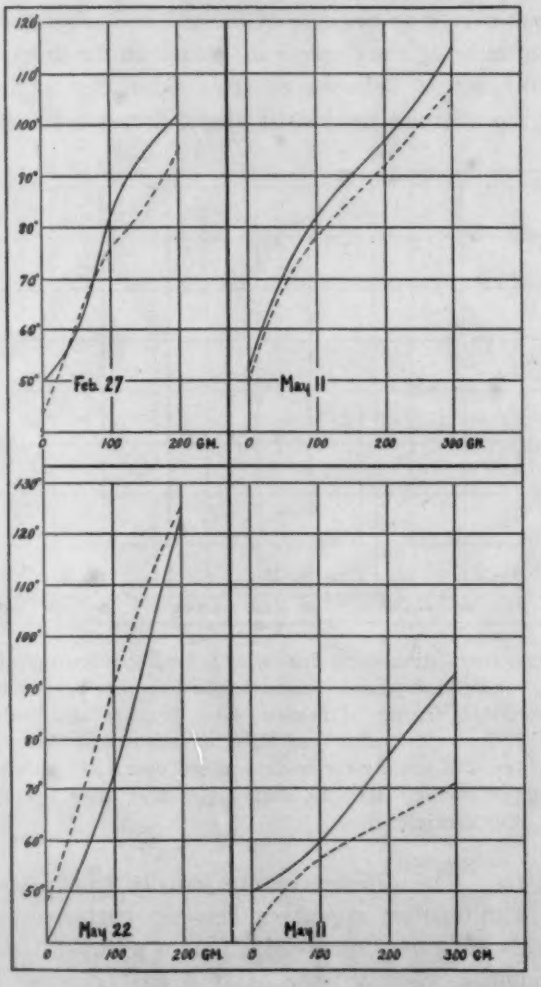

Fig. 2.—Curves correlating elbow flexion with flexing force applied in stellate experiments: abscissae, tension applied to wrist perpendicular to ulna; ordinates, degrees of flexion (described in text); solid line, limb operated on; broken line, control. February 27, three days after operation, measurements made one hour after decerebration; May 11, seventy-six days after operation, upper curves twenty minutes, lower curves three hours after decerebration; May 22, seventy-four days after operation, one and one-half hours after decerebration.

Kerper [9] is employed, the angles being the degree of flexion of the elbow joint; i. e., its departure from 180 degrees. The curves of February 27 show slightly greater flexion (signifying less rigidity) on the side operated on, especially with the maximum flexing force. The same is shown in both pairs of curves of May 11, especially in the second pair, made an hour and a half after the first. The curves of May 22, on the other hand, show more rigidity in the leg operated on. Figure 3 shows curves from three of the abdominal sympathetic experiments, the angles being the degrees of flexion in the ankle joint. They show slight differences between the two sides, but as in the stellate experiments, the average suggests a slight decrease in rigidity on the

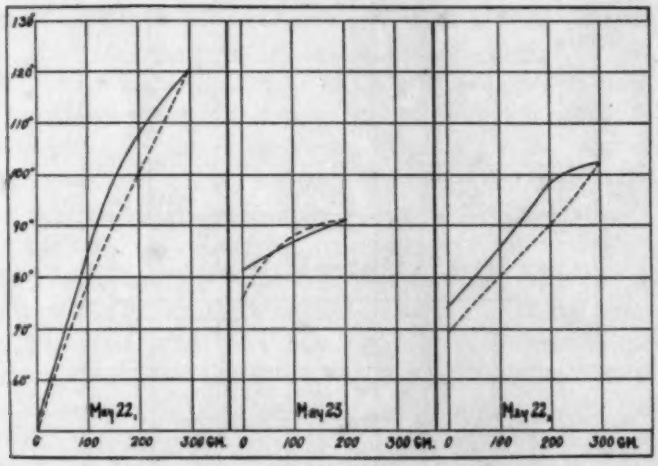

Fig. 3.—Curves correlating ankle flexion with flexing force applied in abdominal sympathetic experiments: abscissae, tension applied to foot perpendicular to metatarsal bones; ordinates, degrees of flexion; solid line, operated limb; broken line, control. May 22, four days after operation, measurements forty minutes after decerebration; May 22, seventy-three days after operation, measurements fifty minutes after decerebration; May 23, sixty-eight days after operation, measurements one hour after decerebration.

side operated on. The differences are usually small, however, compared with the differences appearing between corresponding limbs in different animals or, indeed, between different groups of measurements in the same animal, when a lapse of time has occurred between the measurements.

The results taken as a whole are summarized in the accompanying table. In this table we have included the most complete of the first three experiments, in which decerebration was performed before sympathectomy, and all of the experiments in which these operations were performed in the reverse order. In columns 4-7 are given the

General Summary of Results

Date of Decerebration 1925	Type of Operation	Time in Days	Average Angle in Pair Operated On: 100 Gm. Tension O Degrees	100 Gm. Tension C Degrees	200 Gm. Tension O Degrees	200 Gm. Tension C Degrees	Average Excess Tension for Equal Flexion, per Cent	Mean Deviation	Results of Palpation: Pair Operated On	Results of Palpation: Pair Not Operated On	Summary
Feb. 18	Left stellate	0	35	33	45	42	..	..	Symmetrical; sometimes slightly less	Symmetrical	0*
Feb. 27	Left stellate	3	82	76	102	95	15	24	Symmetrical; slight fluctuations	Symmetrical	+
March 2	Left stellate	6	59	56	66	70	4	12.5	Symmetrical; varying to more	Symmetrical	—
May 15	Left stellate	7	..	..	...	...	25	25	Symmetrical	Symmetrical	0 or +
May 18	Left stellate	10	79	68	90	95	13	31	Symmetrical	Symmetrical	0 or +
June 11	Left stellate	10	97	91	135	123	15	10	Symmetrical; sometimes slightly less	Symmetrical	+
June 11	Right stellate	27	69	70	101	127	16	12	Symmetrical	Slightly less in right leg	0
May 23	Right stellate	51	..	..	...	...	..	..	Symmetrical	Symmetrical	0
May 22	Left stellate	74	73	90	123	125	—2	15	Symmetrical; varying to more	Variable	—
May 11	Left stellate	76	71	67	88	78	3.5	31	Symmetrical	Variable, sometimes less in left leg	+
May 28	Left stellate	80	..	..	...	...	100†	..	Symmetrical; varying to less	Variable; usually symmetrical	0 or +
May 22	Left abdominal	4	83	79	108	100	—2 †	..	Symmetrical, at one time very slightly more	Symmetrical; with variation	0
June 12	Left abdominal	11	..	..	...	...	—33	34	Symmetrical; varying to more	Symmetrical; varying to more in left	—
May 23	Left abdominal	68	89	88	91	91	25	11	Less; later approaching symmetry	Symmetrical	+
May 22	Left abdominal	73	85	80	98	90	4	12	Symmetrical	Symmetrical	0

* In this experiment the corresponding averages for the pair of limbs not operated on (hind legs) were as follows: for 100 Gm., left 58 degrees, right 45 degrees; for 200 Gm., left 75 degrees, right 47 degrees.

† There was only a single pair of measurements of this type in this experiment.

Column 3 shows the interval between sympathectomy and decerebration. Columns 4 to 7 show averages of angles of flexion on the two sides with equal tension. O signifies side operated on; C, control. Column 8 gives average percentage of excess tension on the more rigid side when limbs were pulled to equal flexion; + signifies less tension required on side operated on; — signifies the reverse. Column 9 gives the mean deviation of all measurements from the averages given in column 8. Columns 10 and 11 are condensed results of observation by palpation, for the pairs of limbs operated on and not operated on, respectively. "More" and "less" refer to rigidity in the limb operated on as compared with its mate. Column 12 summarizes results of all methods combined, + signifies definite preponderance in favor of decreased rigidity in limb operated on, — signifies the reverse. 0 signifies symmetry throughout or approximately equal evidence pointing in opposite directions; 0 or +, slight or doubtful preponderance of positive evidence.

averages of measurements of the significant angles. As in the case of figures 2 and 3, the angles express the flexion of elbow or ankle. The range of variation among individual measurements making up these averages was in the neighborhood of 20 degrees.

In column 8, showing comparisons of tensions which induced equal amounts of flexion on the two sides, each number represents the average difference for all measurements made during the course of the experiment. The difference is expressed as the percentage of excess tension on the side on which it was greater. In almost every experiment there were both positive and negative differences in the individual measurements and widely divergent values; the range of variation is indicated in column 9.

The next two columns give the results of comparisons made merely by palpation, i. e., without the spring balance. By comparing the results in columns 4, 5, 6, 7 and 8 with those in column 10 we can form an idea of the amount of agreement between the quantitative measurements and the judgments based on feeling.

The final column summarizes the results of both quantitative measurement and palpation for each experiment. Four experiments gave positive results, that is, supporting Hunter's view; while three were negative, pointing to the opposite conclusion. Eight experiments showed symmetry or at most slight and doubtful positive results, making with the three negative experiments in the table and the two other preliminary experiments not tabulated, a majority of thirteen out of seventeen, which failed to support Hunter's view.

In appraising these results it should be emphasized that we found a strong tendency during supposedly symmetrical palpation to focus the attention on the limb operated on, and in making the comparison to manipulate it more than its mate. As already stated, this manipulation tends to decrease the rigidity in consequence of the lengthening reaction described by Sherrington. It therefore constitutes a highly deceptive source of error which may account for the tendency to detect a lessening of tonus on the side operated on.

It was noted in the introduction that Hunter insisted on plasticity in tonus, revealed by the shortening and lengthening reactions, as the special property lost in consequence of sympathectomy. In most of our experiments the limbs were examined with especial reference to plastic tonus; that is, we noted whether the lengthening and shortening reactions could be evoked and whether the limb operated on differed in this respect from its mate. Our observations showed regularly that these reactions can be evoked in sympathectomized limbs, and in general we found no difference in this respect between the limb operated on and its mate. In two instances there was slightly more plastic tonus on the side operated on.

The animal decerebrated May 23, sixty-eight days after abdominal operation, showed the largest and most consistent difference of the sort found by Hunter. We therefore saved specimens of the extensor muscles under observation on the two sides and had them sectioned and stained with hematoxylin and eosin. Dr. Stanley Cobb examined these sections and reported both specimens normal and indistinguishable, as far as he was able to observe, under the microscope.

The animal decerebrated March 2, six days after the stellate operation, is an example of the fortuitous changes of rigidity which render difficult a strict quantitative treatment of this problem. This animal for

Fig. 4.—Appearance of animal two hours after decerebration, six days after left stellate operation, showing persistent maintenance of *greater* rigidity in limb on which operation has been performed.

a time showed symmetrical rigidity on the two sides. About an hour after decerebration a marked and persistent increase in rigidity appeared on the side operated on as compared with the control. The animal was placed on its back, whereon the limb operated on persistently retained its posture of extension against gravity, while the limb not operated on dropped into a flexed position in the manner described by Hunter as typical for the limb operated on. This paradoxic condition lasted for more than an hour, during which time the photograph shown in figure 4 was taken. The picture would be quite typical of the condition described by Hunter and Royle, but for the fact that in this case it was the limb operated on, and not the control, whose rigidity maintained the extended.

posture against gravity. The characteristic change in the nictitating membrane eliminated the possibility of any error as to which was the operated side.

On the whole our results show a slight preponderance of readings which indicate less rigidity on the side operated on. A careful examination of the table, however, shows that the differences between the two sides are usually small compared with the differences between the absolute measurements in the series of experiments. And it should be emphasized that most of the figures in the table are averages made up of individual figures showing fairly wide variation. In other words, if there is any loss of rigidity traceable to sympathectomy it is small compared with the fluctuations due to other causes. Since the majority of our observations show almost perfect symmetry of rigidity after, as well as before, sympathectomy, and since observations showing actually greater rigidity on the side operated on are not uncommon, it is fair to conclude that if sympathectomy has any effect at all on decerebrate rigidity it is at most insignificant. We cannot positively exclude such an effect; neither can we conclude that our data, or indeed any other with which we are acquainted, suffice to indicate its existence.

Recalling that Hunter emphasized the need of waiting days or even weeks after sympathectomy before decerebrating, let us turn to the table to see whether there was any tendency for the effect he described to increase as the interval increased. The observations are arranged in the order of the number of days elapsing between sympathectomy and decerebration, first in the case of the stellate and then of the abdominal operations. No such correlation appears, and we are therefore unable to verify the existence of any delayed effect such as has been alleged.

In three of the animals decerebrated after unilateral sympathectomy we compared the electromyograms of the extensor muscles in the limb operated on and in its mate. Records were made of rigidity, undisturbed by applied tension, and of the myotatic responses to forced flexion, equal tensions being applied to the two sides in alternation. On the intact side there was no clear evidence of tonus without action currents; that is, the apparent amplitude of the action currents in general corresponded with the tension which the rigidity was resisting. Furthermore, no regular difference in this respect was found between the two sides.

COMMENT

Our evidence, as well as the theoretic considerations outlined in the introduction, lead us to substantially the same view that has been set forth by Walshe.[26] Perhaps the strongest reason for supposing that the sympathetic nerves play a significant rôle in maintaining tonus in skeletal

26. Walshe, F. M. R.: Med. Science **12**:437 (Sept.) 1925.

muscle is the histologic evidence for the existence of certain muscle fibers innervated by these. It is perhaps premature to accept these anatomic findings as conclusively established for limb muscles, but they seem to have been supported by degeneration experiments in the hands of such competent workers that their validity is probable in the muscles that have been examined. If an appreciable number of skeletal muscle fibers in the limbs are innervated in this way, it is hard to conceive of such a neuromuscular mechanism existing without functional significance. Sympathetic innervation in itself suggests the possibility of a relatively sluggish type of contraction. Moreover, several workers [27] have shown that the red fibers respond more sluggishly than the white, both as regards their action currents and their contraction. The postulation of a catch mechanism for plastic tonus, distinct from the contractile mechanism, is a natural consequence of the superficial resemblance between plastic tonus and the behavior of the molluscan adductor. Needham [16] suggests that the red fibers may possess a catch mechanism for tonus and a separate contractile mechanism for shortening, whereas the white fibers possess only the contractile mechanism. How can we reconcile such mechanisms with the fact that a nerve when excited responds with only one kind of impulse, and the regular consequence of this is a contractile response in the innervated muscle—a response that cannot be graded in quality or quantity except so far as the frequency of excitation or the load encountered is altered? A catch mechanism in the red fibers, distinct from their contractile mechanism, would require either a separate neural path or a property in the muscle of responding in a special way to a limited range of frequencies in the nerve impulses. An obstacle to assigning the alleged sympathetic function to the red fibers is the observation of Hay [28] that they are innervated by medullated nerve fibers. A much simpler view than that of dual function would be that each muscle fiber, whether red or white, slender or coarse, has only one type of functional response, but that such fibers as have sympathetic connections contract more sluggishly than those innervated directly from the spinal cord. On this view we should expect the muscle as a whole to contract and relax more briskly after sympathectomy, since the quicker white fibers are still in action and the slower fibers have ceased to function. If then we regard tonus simply as a nicely balanced and sustained series of proprioceptive reflexes, as Cobb contends, then throwing the more sluggish fibers out of action should render tonus less plastic. If the limb muscles really possessed the alleged sympathetic innervation, it is quite possible that this would be the case, but our results show that the change, if it occurs at all, is insignificant. This conclusion is rein-

27. Cobb (footnote 1, p. 520).

28. Hay, J.: Liverpool M. & Chir. J. **21**:431, 1901.

forced by the recent evidence of Huggett and Mellanby [29] on the absence of influence on tonus of those drugs affecting autonomic endings.

Hunter contended that the effect of sympathectomy on tonus becomes progressively greater for many days after the operation. We would again emphasize that such a progressive change, if established, would prove that the loss of tone was not directly due to the cessation of motor-nerve impulses, since these impulses must cease to flow immediately after section of the nerve. The effect would necessarily depend on secondary causes. If the loss of tone really occurred, it might conceivably result because disuse would render the fibers softer and more extensible and therefore less prone to resist deformation of the muscle as a whole, or it might be due to circulatory changes. On reference to the accompanying table it will be seen that the two most definitely positive experiments in our series were on animals decerebrated three and ten days after sympathectomy. On the other hand, we find two negative experiments at six and eleven days, and two symmetrical experiments at four and seven days. These observations point to the view that we are dealing rather with haphazard or chance fluctuations than with any definite results of the operation. Certainly no tendency to a progressive increase in the loss of tonus appears in our table.

Physicians and surgeons who have observed cases of spasticity in which ramisection was performed have described them to us. In one case, at least, careful observation before and after operation showed no relief from the spastic condition. In two cases, on the other hand, the operation seemed to produce some degree of temporary and even permanent improvement. Such cases and those reported by Royle, together with the apparently positive experiments on goats, appear to be the chief facts in favor of Hunter's view. How are we to reconcile them with the apparent lack of physiologic basis in our experiments and in those of the majority of other workers? Of our experiments those which seemed to show definite results of the sort described by Hunter and Royle were few. The positive results of others and the surgical successes have also been few. In view of the many possible sources of error in the interpretation of results, and especially in consideration of other possible causes of improvement in the surgical cases—such as exercises, mental suggestion and extra good care—it is perhaps reasonable to conclude that the surgical successes are not much more significant than the small percentage of apparently positive experiments in our series. Looking over the sum total of results from both surgical operations and physiologic experiments reported by a considerable number of workers, we are led to believe that the alleged effects of sympathectomy,

29. Huggett, A. St. G., and Mellanby, J.: J. Physiol. **60**:8, 1925.

when present, are due to extraneous circumstances and uncontrolled causes rather than to the direct effects of removing the sympathetic innervation.[30]

SUMMARY

1. Certain investigators have contended that "contractile" and "plastic" tonus in skeletal muscle are two distinct functions, depending respectively on the cerebrospinal, medullated nerve fibers and on those arising from the sympathetic chain. This theory we find to be without adequate experimental foundation, and, in its extreme form, inconsistent with the known facts of nerve-muscle physiology.

2. In a series of cats we have cut the sympathetic innervation of one limb, either immediately after or at intervals varying from three to eighty days before decerebration. In these animals we have compared the decerebrate rigidity of the limb involved in the operation with that of the other limbs, measuring with spring balances the tension required to force various degrees of flexion, and noting the "plastic" feature of rigidity.

3. The results have shown wide variations in rigidity, depending on postures imposed on the animal, and almost as great variations apparently dependent on conditions of the experiment not subject to control. Comparison of the operated limb with its mate usually shows almost perfect symmetry, i. e., no appreciable difference. Sometimes there is less rigidity on the side operated on, sometimes more. Averaging the measurements of the entire series showed slightly less rigidity on the side operated on; but this difference was small compared with the individual fluctuations in both directions making up the average.

4. We conclude that if there is any loss of tonus in consequence of the operation it is insignificant. Certainly decerebrate rigidity persists,

30. Since this article was written, an article by S. W. Ranson (J. Comp. Neurol. **40**:1 [Feb.] 1926) has appeared in which a lessening of decerebrate tonus, following application of nicotine to spinal ganglions, is cited in support of the theory of plastic and contractile tonus. This article contains no proof of a qualitative change in tonus, and the results might be explained in other ways not involving the assumption of two types of tonus. Another recent paper by Kuntz and Kerper (Am. J. Physiol. **76**:121, 1926) ends to support the conception of a plastic function mediated by the sympathetic nerves. Their results are complicated by the presence of the intact cerebrum. A possible explanation may lie in L. A. Orbeli's observation (J. Petrograd M. Inst. **6**:8, 1923) which suggests a chemical effect of sympathetic nerve impulses counteracting fatigue and thus aiding sustained contraction under conditions tending to produce fatigue. Still another paper by F. D. Coman (Bull. Johns Hopkins Hosp. **38**:163 [March] 1926), which has appeared since our article was written, furnishes three lines of evidence against the view that postural tonus of skeletal muscle is developed or maintained by sympathetic nerves.

at least approximately undiminished, and manifests its plastic features after sympathectomy.

5. This conclusion removes the alleged physiologic basis for the surgical operation of ramisection as a cure for spasticity. If patients are in reality improved in consequence of this operation, it is probably due to some incidental feature of their treatment, and not to the interruption of nerve impulses arising in the sympathetic nervous system.

THYROID DISTURBANCES

CLINICOPATHOLOGIC STUDY OF THREE HUNDRED INSTANCES *

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The study of thyroid disease has progressed in a manner similar to that of kidney disturbances. Each has resulted in the introduction into the literature of many classifications. For this reason antagonistic views have always existed between clinicians and pathologists concerning the study of irregularities in these organs.

While, therefore, the literature of the thyroid gland is considerable, comprehensive clinicopathologic analyses that might mitigate these differences have not been found. Most pathologic studies of the thyroid gland have been either in the form of simple academic outlines of pure pathology or as histopathologic studies correlated with certain of the more striking symptoms. One of the earliest classifications of thyroid changes in relation to symptoms was that proposed in 1908 by Wilson,[1] who found that general changes in the thyroid parenchyma paralleled the character and intensity of symptoms produced. Later Wilson [2] differentiated the pathologic changes in simple and exophthalmic goiters, subdividing the former group into diffuse and nodular types. Shepherd and Duval,[3] writing in 1909, reported histopathologic changes found in a series of fifty-nine cases, but concluded that no cytologic changes could be regarded as specific for any special type of disease of the thyroid gland. Following this Marine and Lenhart [4] introduced a classification based on the principles of pure pathology. While the details are accurate it is perhaps too academic for clinical application. Similarly, McCarty [5] in 1912 published an elementary analysis of histologic findings in a large number of cases, but without any conclusions as to their significance or possible application. About 1919, Plummer [6] pointed out that hyperthyroidism could be divided into two separate and distinct types each due to a different pathologic change in

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1. Wilson, L. B.: Am. J. M. Sc., December, 1908.
2. Wilson, L. B.: Surg., Gynec. & Obst., June, 1908, pp. 558-602; Am. J. M. Sc. **146**:781-790, 1913.
3. Shepherd and Duval: Tr. Am. S. A. **27**:56, 1909.
4. Marine and Lenhart: Arch. Int. Med. **7**:506-535, 1911.
5. McCarty, Y. C.: New York State J. Med. **12**:595, 1912.
6. Plummer, H. S.: Am. J. M. Sc. **146**:790, 1913.

the thyroid gland; namely, diffuse hypertrophy and hyperplasia, and adenoma. A later clinical classification by Williams [7] differentiated simple and toxic goiter. In the same year, Else [8] introduced a more comprehensive classification, segregating a cardiovascular group. In 1922 Goetsch [9] introduced a conception of excessive interstitial hyperplasia which he designed adenomatosis, pointing to it as a factor in mild hyperthyroidism. That these changes are not compensatory or regenerative rather than primarily toxic has never been established. Holst [10] in 1923 offered a simple classification based on gross findings. He agreed with Hellwig,[11] who had traced the steps of development from simple colloid goiter to a typical exophthalmic gland, that all cases of hypersecretion are conditions of hyperthyroidism and not dysthyroidism. Biedl [12] in 1924 summarized the European conception of thyroid disturbance as follows: (1) simple diffuse struma; (2) simple nodular adenoma, and (3) parenchymatous hyperplastic thyroid. He maintained that true Basedow's disease is seen only in subjects with status thymicolymphaticus. More recently Williamson and Pearse [13] have introduced a classification based on their conception of thyroid structure. It would seem that detailed observations have been ascribed an unestablished importance in their outline.

Much of the divergence in views held is undoubtedly due to the incomplete knowledge of the structure and physiology of the thyroid gland. In spite of the splendid work of Bensley [14] on the opossum in which he pointed out the mode of secretion, transcellular or intercellular migration, and colloid storage, much remains obscure as to the manner in which the gland responds to stimuli. There is a question as to whether the whole gland may become active in a diffuse way or in a patchy focal reaction. The relative stability of the hormone containing colloid also is unsolved. It is conceivable that an older colloid may hold the active principle with greater tenacity than that more recently formed and stored. The resistance of such colloid stability to demanding stimuli may lead to more responsive portions yielding an overproduction. Then, too, there remains for determination the secretory power of thyroid epithelium as affected by such colloid storage, since the latter in itself may possibly lead to cell atrophy and atony. Williamson and Pearse [15] in their recent

7. Williams, C.: Am. J. M. Sc. **161**:223 (Feb.) 1921.
8. Else, J. E.: Northwest Med. **20**:118 (May) 1921.
9. Goetsch, E.: Endocrinology **6**:59-72 (June) 1922.
10. Holst, J.: Acta chir. Scandinav. **4**:1-91, 1923.
11. Hellwig, A.: Deutsch. med. Wchnschr. **48**:420, 1922.
12. Biedl, A.: Ann. Clin. Med. **3**:444 (Dec.) 1924.
13. Williamson and Pearse: J. Path. & Bacteriol. **28**:361-389 (April) 1925.
14. Bensley: Am. J. Anat. **19**:37 (Jan.) 1916.
15. Williamson and Pearse: J. Path. & Bacteriol. **26**:459, 1923.

work on the structure of the thyroid have offered some interesting data as to the nature of the tubuli, the vascular relationship and the manner in which the solid tubuli develop colloid containing alveoli. It is their opinion that the active agent is delivered into lymph channels. This is in disagreement with others who regard the veins as being the chief carrying channels of the hormone. The question as to whether the thyroid gland can produce anything but a specific hormone in normal, deficient or excessive amounts has never been fully answered.

Although there have been conflicting interpretations of the thyroid in health and disease, there are outstanding facts of common observation. It is generally agreed that the gland varies markedly in size and shape and that clinically it ranges in symptomatology from cretinism and myxedema to hypersecretion or perversion of function as the case may be. In our experience we have been able to group the surgically removed portions, or entire glands, according to their gross characteristics and salient, predominating microscopic pathologic condition as follows:

PATHOLOGIC CLASSIFICATION NORMAL OR ENLARGED GLAND WITH OR WITHOUT INCREASED OR DECREASED ACTIVITY

I. Diffuse parenchymatous hyperplasia.

1. Gross examination: Compact, ischemic, grayish white and colloid free.
2. Microscopic examination:
   a. Hyperplasia and hypertrophy of epithelium.
   b. Peripheral or general vacuolization of colloid.
   c. Dilatation of lymph channels and engorgement of blood vessels.
   d. Variable increase in the supporting stroma with or without round cell infiltration.

II. Diffuse adenomatous hyperplasia.

1. Gross examination: Diffuse reddish brown gland without noticeable nodularity or accentuation of lobular markings; variable amount of colloid.
2. Microscopic examination:
   a. Focal changes similar to Group I.
   b. Normal or colloid stretched alveoli.
   c. Focal hyperplasia and hypertrophy of epithelium.
   d. Interalveolar hillocks or intra-alveolar papillomatous projections.
   e. Focal round cell collections of pseudolymph nodes.
   f. Focal increased vascularity and dilated lymph channels.

III. Nodular adenomatous hyperplasia.

1. Gross examination: Variable nodular accentuation of the lobular markings with or without excessive colloid storage, cystic degeneration, hemorrhage, scarring or lime salt deposit. The color usually varied with the regressive changes.

2. Microscopic examination:
   a. Focal cytologic changes similar to these found in Groups I and II; compensatory.
   b. Characteristic retrogressive changes.
   c. Areas of adenomatosis.

IV. Solitary adenoma.

1. Gross examination: Variable in size; circumscribed; solitary or multiple; grayish white to dark reddish brown; solid, cystic or colloid filled. Regressive changes may be present.
2. Microscopic examination:
   a. All stages of fetal types of alveoli.
   b. Peripheral pseudocapsule formation with round celled infiltration and compressed alveoli.
   c. Focal neighboring hyperactive areas in adjoining parenchyma.
   d. Neighboring areas of adenomatosis.

V. Neoplasms.

VI. Inflammations.

1. Pyogenic.
2. Infectious granuloma.

While the gross divisions of the portions of the thyroid removed are rather easily affected according to the foregoing outline, there are numerous instances of the shading of one group into the other. Such glands of border-like nature must be relegated to the group according to the dominancy of certain classifying characteristics. More detailed separations are as futile here as they are in kidney disease.

In the microscopic analysis it is important to establish histologic criteria of activity or rest. We are certain of one thing, namely, that the histologic appearance of the gland in Group 1, diffuse parenchymatous hyperplasia—so-called exophthalmic goiter (Fig. 1)—is just as definite as are the gross and clinical manifestations. This is conceded to be an entity in all respects. We may therefore safely assume that the microscopic pattern found here is one resulting from the production and the delivery of thyroid hormone or its by-products into the lymphatics or veins. There is evidence to show that cellular hypertrophy and hyperplasia, peripheral vacuolization of colloid, dilated lymph channels and veins and the resulting alveolar distortion occur in the order named, and are natural steps in the mechanism of function of any ductless gland and are accompanied by an increased blood supply to the part. Prolonged activity probably leads to the necessity for more supportive stroma and the appearance of special inflammatory absorption reactions consisting of lymph cell collections or pseudolymph nodes (Fig. 2). Finally destruction with areas of adenomatosis (Fig. 3)—probably reconstruction—or a gradual reversal of the process occurs. When the latter is viewed a double row of cells lining alveoli, small papillomatous projec-

tions into large colloid filled alveoli and interalveolar hillocks may be seen (Figs. 4 and 5). The disturbance finally becomes patchy. With such histologic criteria as these in mind one can analyze the thyroids of various groups and gage their relative activity in surprising agreement with the clinical manifestations. One can say with a fair degree of accuracy as to whether a given gland has produced no, slight, moderate, marked, or extreme symptoms.

In view of the foregoing observations it would seem to us that thyroid activity is generally spotty. Excessive colloid storage, nodular modification of structure, inflammatory atrophies, and neoplasm in one part may reflect an increased necessity for activity in another or adjacent portion.

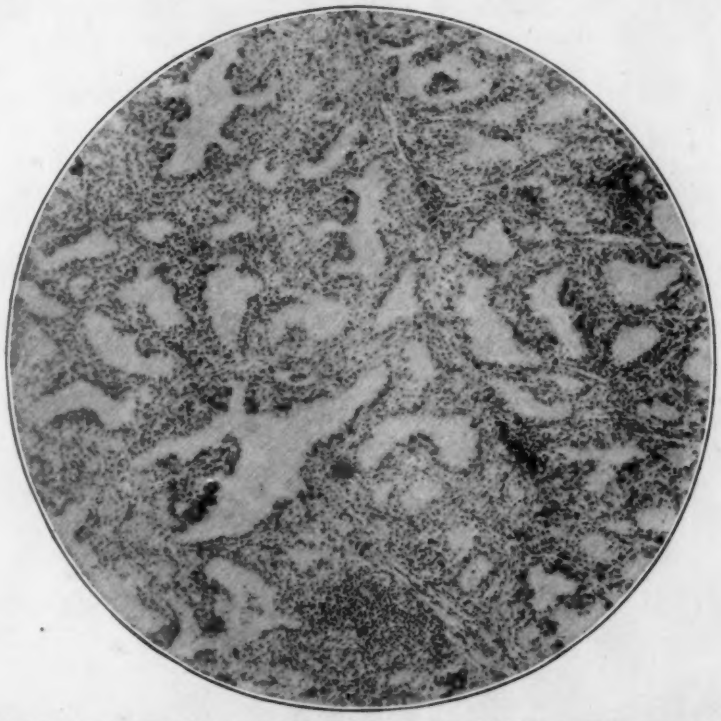

Fig. 1.—Appearance of structural design in the diffuse parenchymatous hyperplasia, so-called exophthalmic goiter.

With these pathologic conditions in mind we deemed it of sufficient merit to analyze 300 instances of thyroid disturbances in the light of the available clinical data in each case (accompanying table).

COMMENT ON TABLE

It will be seen that thirty-eight of these, or 12.6 per cent., fall in Group 1 (diffuse parenchymatous hyperplasia), 108, or 35 per cent., in Group 2 (diffuse adenomatous hyperplasia), 102 in group 3 (nodular

Pathologic Grouping and Comparison of Composite Clinical Data in Three Hundred Cases

Clinical Data	Pathologic Grouping—Normal or Enlarged Thyroid With or Without Increased or Decreased Activity																			
	Group 1 Diffuse Parenchymatous Hyperplasia			Group 2 Diffuse Adenomatous Hyperplasia			Group 3 Nodular Adenomatous Hyperplasia			Group 4 Solitary Adenomas			Group 5 Neoplasms			Group 6 Inflammatory Processes		
	No.		Per Cent.	No.		Per Cent.	No.		Per Cent.	No.		Per Cent.	No.		Per Cent.	No.		Per Cent.
Total cases	38		12.6	108		36	102		34	41		13.6	7		2.3	4		1.3
Age	1	From 0 to 20 yrs.	3	4	From 0 to 20 yrs.	3	3	From 0 to 20 yrs.	3	1	From 0 to 20 yrs.	3	0	From 0 to 20 yrs.	3	1	From 0 to 20 yrs.	25
	9	From 20 to 30 yrs.	23	29	From 20 to 30 yrs.	27	10	From 20 to 30 yrs.	10	7	From 20 to 30 yrs.	18	1	From 20 to 30 yrs.	14	0	From 20 to 30 yrs.	0
	12	From 30 to 40 yrs.	31	30	From 30 to 40 yrs.	28	26	From 30 to 40 yrs.	26	10	From 30 to 40 yrs.	26	2	From 30 to 40 yrs.	28	1	From 30 to 40 yrs.	25
	12	From 40 to 50 yrs.	31	25	From 40 to 50 yrs.	23	29	From 40 to 50 yrs.	29	13	From 40 to 50 yrs.	34	3	From 40 to 50 yrs.	42	1	From 40 to 50 yrs.	25
	3	From 50 to 60 yrs.	9	13	From 50 to 60 yrs.	12	20	From 50 to 60 yrs.	20	6	From 50 to 60 yrs.	16	0	From 50 to 60 yrs.	0	1	From 50 to 60 yrs.	25
	1	From 60 to 70 yrs.	3	7	From 60 to 70 yrs.	6	10	From 60 to 70 yrs.	10	4	From 60 to 70 yrs.	10	0	From 60 to 70 yrs.	0	0	From 60 to 70 yrs.	0
Sex	29	Females	80	86	Females	80	91	Females	91	36	Females	89	4	Females	58	2	Females	50
	9	Males	20	22	Males	20	9	Males	9	5	Males	11	3	Males	42	2	Males	50
Location	26	Oregon	68	80	Oregon	88	82	Oregon	82	35	Oregon	85	5	Oregon	72	4	Oregon	100
	10	Washington	26	10	Washington	12	11	Washington	11	3	Washington	7	1	Washington	14			
	1	Idaho	2	18	Unknown	..	2	Idaho	2	2	Colorado	5	1	British Columbia	14			
	1	Utah	..				3	Montana	3	1	Hawaii	2						
Rate of development	17	Unknown	47	24	Unknown	22	39	Unknown	58	22	Unknown	47	4	Unknown	38	2	Unknown	50
	8	Gradual	22	32	Gradual	38	26	Gradual	41	12	Gradual	63	2	Gradual	66	2	Gradual	50
	7	Adolescent	18	42	Adolescent	50	34	Adolescent	54	6	Adolescent	32	1	Adolescent	33			
	6	Fast	13	10	Fast	12	3	Fast	4	1	Fast	5	0	Fast	0			
Marital state	29	Married	80	86	Married	81	81	Married	81	33	Married	80	3	Married	42	2	Married	50
	9	Single	20	22	Single	20	19	Single	19	8	Single	20	4	Single	58	2	Single	50
Pregnancies	15	From 1 to 4	39	40	From 1 to 5	37	54	From 1 to 5	54	23	From 1 to 6	54	3	From 1 to 6	42	1	From 1 to 3	50
	23	None	61	68	None	63	48	None	48	18	None	46	4	None	58	3	None	75
Miscarriages	6	Of 15	40	13	Of 40	32	7	Of 54	13	8	Of 23	34	1	Of 3	33	1	Of 1	100
Previous conditions	10	Influenza	28	35	Influenza	32	14	Influenza	14	10	Influenza	24	2	Influenza	28	2	Influenza	50
	20	Measles	56	70	Measles	65	43	Measles	43	17	Measles	72	5	Measles	72	2	Measles	50
	18	Mumps	47	50	Mumps	46	27	Mumps	27	8	Mumps	19	6	Mumps	84	2	Mumps	50
	3	Typhoid	7	13	Typhoid	12	3	Typhoid	3	4	Typhoid	9	1	Malaria	14	1	Typhoid	25
	8	Tonsillitis	21	5	Tonsillitis	5	15	Tonsillitis	15	12	Tonsillitis	30	2	Rheumatism	28	1	Tuberculosis	25
	2	Scarlet fever	5	6	Scarlet fever	6	2	Scarlet fever	2	5	Scarlet fever	12	0	Scarlet fever	0	2	Scarlet fever	50
	12	Whooping cough	31	30	Whooping cough	28	27	Whooping cough	27	7	Whooping cough	17	2	Whooping cough	28	1	Whooping cough	25
	2	Smallpox	15	8	Smallpox	8	8	Smallpox	8	2	Smallpox	5	0	Smallpox	0	1	Smallpox	25
	5	Pneumonia	14	7	Diphtheria	7	2	Pneumonia	2							1	Syphilis	25

Systolic blood pressure	9	Unknown	26	27	Unknown	25	32	Unknown	32	15	Unknown	37	1	Unknown	14	1	Unknown	25
	2	From 100 to 120	5	20	From 100 to 120	23	14	From 100 to 120	20	7	From 100 to 120	27	1	From 100 to 120	17	0	From 100 to 120	0
	6	From 120 to 130	15	19	From 120 to 130	22	9	From 120 to 130	13	6	From 120 to 130	23	0	From 120 to 130	0	1	From 120 to 130	25
	4	From 130 to 140	10	18	From 130 to 140	21	10	From 130 to 140	14	2	From 130 to 140	27	1	From 130 to 140	17	0	From 130 to 140	0
	7	From 140 to 150	18	15	From 140 to 150	14	10	From 140 to 150	14	7	From 140 to 150	27	1	From 140 to 150	17	0	From 140 to 150	0
	2	From 150 to 160	5	9	From 150 to 160	8	11	From 150 to 160	16	2	From 150 to 160	7	0	From 150 to 160	0	0	From 150 to 160	0
	8	From 160 to 190	21	10	From 160 to 190	9	16	From 160 to 210	23	2	From 160 to 190	7	3	From 160 to 190	50	2	From 160 to 190	50
Pulse pressure	9	Unknown	26	27	Unknown	25	38	Unknown	30	15	Unknown	37	1	Unknown	14	1	Unknown	25
	29	Known	74	81	Known	75	72	Known	72	26	Known	63	6	Known	86	3	Known	75
							1	From 20 to 30	2									
	0	From 30 to 40	0	3	From 30 to 40	4	8	From 30 to 40	12	4	From 30 to 40	15	0	From 30 to 40	0	0	From 30 to 40	0
	3	From 40 to 50	10	3	Form 40 to 50	4	12	From 40 to 50	17	3	From 40 to 50	11	0	From 40 to 50	0	0	From 40 to 50	0
	4	From 50 to 60	14	13	From 50 to 50	16	13	From 50 to 60	18	11	From 50 to 60	42	3	From 50 to 60	50	1	From 50 to 60	33
	7	From 60 to 70	24	29	From 60 to 70	36	15	From 60 to 70	20	3	From 60 to 70	11	0	From 60 to 70	0	1	From 60 to 70	33
	4	From 70 to 80	14	15	From 70 to 80	18	10	From 70 to 80	14	2	From 70 to 80	10	1	From 70 to 80	17	0	From 70 to 80	0
	11	From 80 to 90	38	13	From 80 to 90	16	11	From 80 to 90	16	3	From 80 to 90	11	2	From 80 to 90	33	1	From 80 to 90	33
Associated conditions	2	Dyspnea	5	4	Dyspnea	4	17	Dyspnea	17	9	Dyspnea	22	1	Dyspnea	14	1	Dyspnea	25
	2	Exophthalmic	5	2	Exophthalmic	2	3	Exophthalmic	3	0	Exophthalmic	0	1	Exophthalmic	14	0	Exophthalmic	0
	1	Insomnia	3	0	Insomnia	0	11	Headaches	11	6	Headaches	15	0	Headaches	0	0	Headaches	0
	1	Diabetes	3	0	Diabetes	0	8	Pressure	8	4	Pressure	10	3	Pressure	42	2	Pressure	50
	6	Tachycardia	15	21	Tachycardia	20	39	Tachycardia	39	12	Tachycardia	30	4	Tachycardia	58	2	Tachycardia	50
	1	Tremor	3	0	Tremor	0	9	Tremor	9	5	Tremor	12	1	Tremor	14	1	Tremor	25
	36	Nervousness	90	85	Nervousness	79	53	Nervousness	53	36	Nervousness	87	4	Nervousness	58	2	Nervousness	50
Basal metabolic rate	2	Unknown	6	28	Unknown	20	59	Unknown	54	20	Unknown	50	2	Unknown	28	3	Unknown	75
	36	Known	94	80	Known	80	45	Known	46	21	Known	50	5	Known	70	1	Known	25
	2	From 10 to 20	5	7	From 10 to 20	9	5	From 10 to 20	11	1	From 1 to 20	5	1	From 10 to 20	20	0	From 10 to 20	0
	2	From 20 to 30	5	22	From 20 to 30	27	17	From 20 to 30	39	8	From 20 to 30	38	1	From 20 to 30	20	1	From 20 to 30	100
	1	From 30 to 40	3	17	From 30 to 40	21	9	From 30 to 40	20	5	From 30 to 40	24	1	From 30 to 40	20	0	From 30 to 40	0
	2	From 40 to 50	5	12	From 40 to 50	15	9	From 40 to 50	20	3	From 40 to 50	15	0	From 40 to 50	0	0	From 40 to 50	0
	29	From 50 to 100	82	22	From 50 to 100	27	5	From 50 to 80	11	4	From 50 to 60	19	2	From 50 to 60	40	0	From 50 to 60	0
Clinical diagnosis	36	Hyperplastic toxic	96	39	Hyperplastic toxic	36	4	Hyperplastic toxic	5	2	Hyperplastic toxic	4	2	Hyperplastic toxic	28	1	Hyperplastic toxic	25
	1	Exophthalmic	2	2	Exophthalmic	2	1	Exophthalmic	1	0	Exophthalmic	0	0	Exophthalmic	0	0	Exophthalmic	0
	1	Adenoma	2	38	Adenoma	36	74	Adenoma	81	35	Adenoma	86	4	Adenoma	58	2	Adenoma	50
	0	Toxic adenoma	0	28	Toxic adenoma	26	12	Toxic adenoma	13	4	Toxic adenoma	10	1	Carcinoma	14	1	Toxic adenoma	25
Amount removed	11	Undetermined	29	27	Undetermined	25	38	Undetermined	37	10	Undetermined	24	0	Undetermined	0	0	Undetermined	0
	27	Determined	71	81	Determined	75	64	Determined	63	31	Determined	76	7	Determined	100	4	Determined	100
	26	Under 100 gm.	96	66	Under 100 gm.	76	34	Under 100 gm.	53	19	Under 100 gm.	63	6	Under 100 gm.	86	4	Under 100 gm.	100
	1	Over 100 (265) gm.	4	15	Over 100 gm.	24	30	Over 100 gm.	47	12	Over 100 gm.	37	1	675 gm.	14	0	Over 100 gm.	0
		Average weight, 50 gm.			Average weight, 65 gm.			Average weight, 70 gm.			Average weight, 74 gm.			Average weight, 143 gm.			Average weight, 50 gm.	

adenomatous hyperplasia), 41 in Group 4 (solitary adenoma with hyperplasia), seven in Group 5 (neoplasm) and four in Group 6 (inflammatory processes). It may be noted that 216, or 70 per cent., fall in the second and third groups.

Age.—Seventy-six per cent. of all the thyroid disturbances came to clinical attention before the fifth decade of life.

The data at hand point to an earlier manifestation of irregularities in Group 1, and in all other groups in proportion to the amount of histologic changes of a similar parenchymatous nature. The age at which

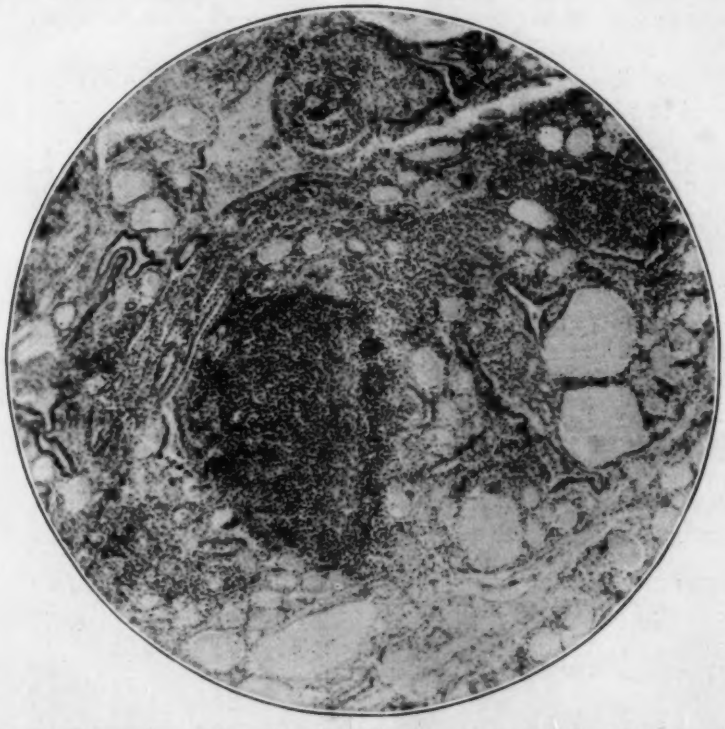

Fig. 2.—Formation of lymph cell collections or pseudolymph nodes in the presence of continued or receding activity.

a patient comes to be treated is of course no criterion as to the time or rate of development. Nodularity in thyroid enlargement evidently requires time, probably being the resultant of many unbalances between storage and the circulatory dispersion of the thyroid hormone.

Sex.—In the first two groups there were four times as many females as males. In two of the groups (Groups 3 and 4), the ratio of males to females is approximately 1 : 10. The proportion here established shows the relationship in the decades of life in which reproduction is most common, the frequency of thyroid enlargement being greatest in

women. The evidence as to sex ratios, in this study, is at variance with other reports from this district concerning men and women of an earlier age. Hall,[16] examining 3,339 students at the University of Washington, found "perceptible, medium and large" thyroids in 374 men out of 2,086 examined (17.94 per cent.) and in 388 women out of 1,253 examined (30.94 per cent.), respectively, a ratio of one man to two women. The average age was about 20 years.

Location.—Most of the patients studied came from regions in Oregon and Washington. It is generally agreed that thyroid disturbance is

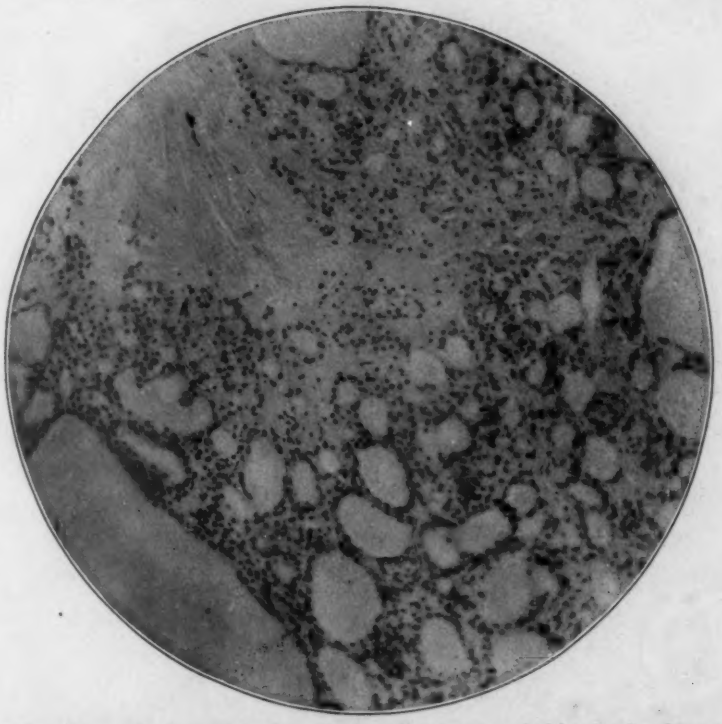

Fig. 3.—Area of adenomatosis near an old scar; such histologic changes are common in regions of the pseudocapsule of nodules or foci of degeneration.

endemic in these two states. It is therefore of interest to note that 12.6 per cent. of all those studied fall definitely in Group 1 (so-called exophthalmic goiter). All gradations between the diffuse parenchymatous hyperplasia group and that of the diffuse adenomatous hyperplasia have been observed. But the incidence of typical so-called exophthalmic goiter given here is of import. There is a scarcity of figures in the literature as to the frequency in nongoitrous districts, so that comparison is not

16. Hall: Northwest Med. **6**:189-193.

possible. Mortality statistics are unreliable for purposes of conclusions as to the prevalence of a given type in a particular community since the death rate was much higher at that time in the so-called exophthalmic variety than in others.

Rate and Time of Development.—Our clinical histories are incomplete concerning this data. In the first two groups a large percentage developed more rapidly than in those of the other groups. It would be of general interest to know the exact details of the manifestations of

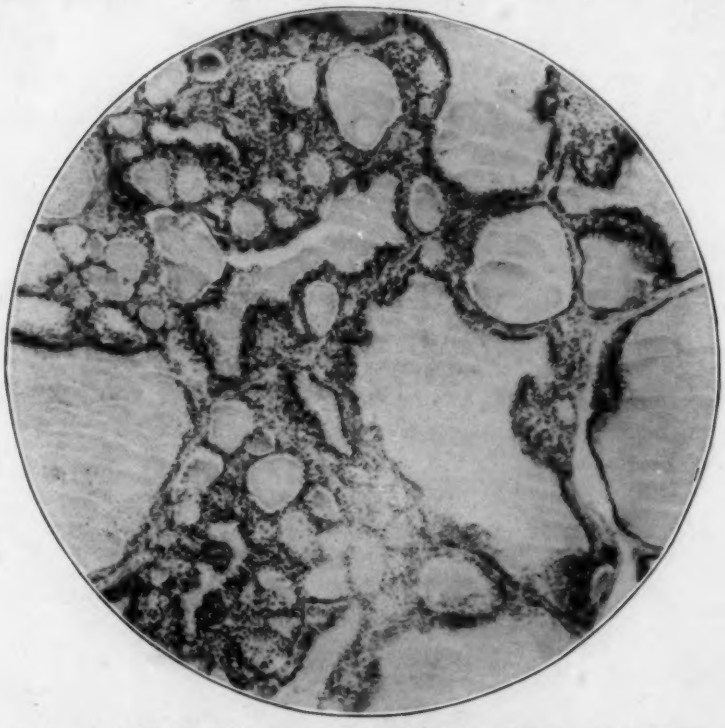

Fig. 4.—Multiple cells lining alveoli and papillary projections.

enlargement that have occurred in each subject presenting himself for treatment.

Marital State.—Approximately 80 per cent. of all the thyroid diseases studied occurred in persons who were married. This high incidence is due to the greater frequency of such disturbances in women who have undergone pregnancies. About half the married women in this series had from one to four pregnancies, in addition to a considerable number of miscarriages. The latter were more frequent in the first two groups. It is probably the result of a combined excessive or modified metabolism and other internal secretion derangements that excite the thyroid in maternity.

Previous Conditions.—Here we have grouped various childhood diseases and incidental infections. All these have induced periodic demands for excess metabolism. It is not possible to pick any one or any group of conditions which may be specifically related to thyroid disturbances. The literature is silent on their rôle. It seems to us that there is to be found here a fertile field for experimentation. There is some suggestion of slow incipient infections, such as tonsillitis, having a more profound and subtle effect on thyroid unbalance than the more acute ones. And

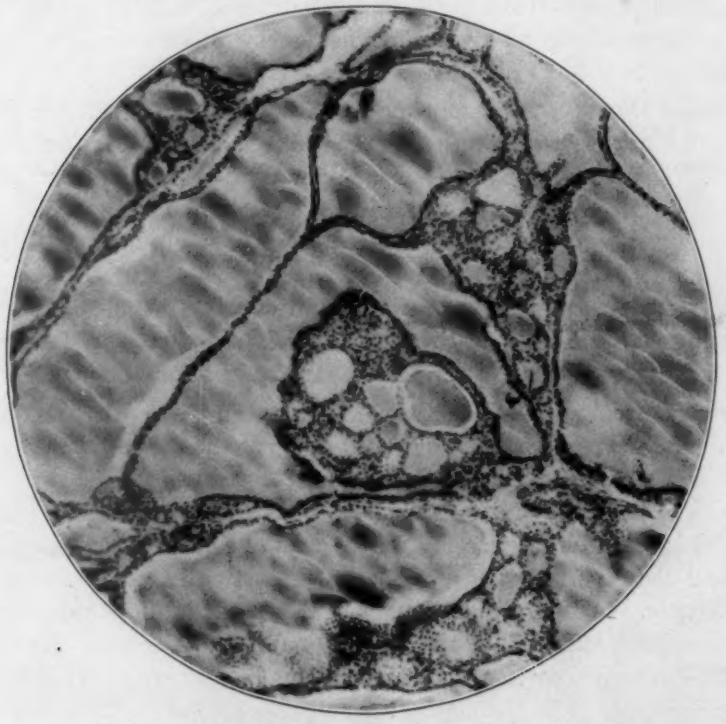

Fig. 5.—Interalveolar hillocks in receding activity.

yet one hesitates to speculate on the appearance of the disturbance in relationship to the time of insults, physiologic or pathologic.

Circulatory Disturbances.—Blood pressure was in general increased. The systolic pressure appeared to have no definite relationship to the type. In respect to the age it was generally higher in the first two groups. In Groups 3 and 4, made up largely of older individuals, such changes as arteriosclerosis and arteriocapillary fibrosis were undoubtedly factors in the average high systolic pressure. In general the pulse pressure is high. In Group 1, 75 per cent. were more than 60; this high average decreased in the other groups. Pulse pressure is apparently much more pronounced in the thyroids exhibiting parenchymatous hyperplasia.

Associated Conditions.—The symptomatology is essentially the same in all types of the disturbances studied, varying only in degree. Dyspnea, tachycardia, nervousness and pressure are the most constant. Diabetes occurred in one instance in the first group. Exophthalmia was seen in the first three groups. It may manifest itself in any thyroid disturbance and is usually associated with emaciation, pointing to excessive metabolism and perhaps other internal secretion disturbances.

Basal Metabolism Rate.—In Group 1 twenty-nine, or 82 per cent., were above plus 50, from three to eight times as high as in any other group. In practically all the instances studied it was above normal (i. e., plus or minus 0 to 15).

Clinical Diagnosis.—Ninety-six per cent. of Group 1 (diffuse parenchymatous hyperplasia) were classified clinically as hyperplastic toxic goiters. This term was applied in 36 per cent. and 5 per cent. of the thyroids in Groups 2 and 3, respectively. Exophthalmic goiter was the diagnosis in a small percentage in the first three groups. Eighty-one per cent. of Group 3 (nodular adenomatous hyperplasia) were classified clinically as toxic adenomas. The clinical classification made independently, at the time of operation, corresponds reasonably well with the natural but somewhat arbitrary pathologic classification adopted here.

Amount Removed.—There has always been more or less speculation as to the effect of the surgical removal of a part of the gland in a given condition. This procedure allows the surgeon to estimate the amount to be removed leaving as far as possible a symmetrical neck. The amount removed is based on the irregularity in size, the evident pathologic condition, and the severity of the symptoms. No two surgeons follow the same technic. In 1898 and later in 1914 Halstead [17] studied the effect of transplantation, removal and amputation of the thyroid gland. He found that the remaining portion of the gland was almost invariably followed by enlargement. The histologic changes were similar to those found in so-called exophthalmic goiter. No such opportunity is afforded clinically. However, the thyroid tissue was weighed immediately after removal and before preservation.

This was done with the idea of checking the end-results in the light of the amount removed and the evidence of disease in the gland. In general, the amounts excised at the present time are smaller than they were several years back, but larger in proportion to the total size of the gland. This is probably because of the education of the public to the dangers of prolonged intoxication from thyroid disturbances and to the need of early consultation of a physician. The amounts removed were smaller in Group 1 and greatest in Group 4.

17. Halstead: Am. J. M. Sc. **147**:56, 1914.

In the foregoing discussion, Groups 5 and 6 were not considered because the number of cases are insufficient to warrant the drawing of conclusions. Six of the neoplasms were carcinomas. One was a solitary papilloma. Of the four inflammatory processes two were tuberculous and two were undetermined, but were associated with chronic pharyngeal and peritonsillar disturbances.

The value of any pathologic classification, from a practical point of view, is valuable only as it may be readily fitted into a clinical concept. It has been of interest to us to note that there are many difficulties in such assorting of thyroid diseases, but that the situation approaches futility when there is an attempt made to give each detail in the morbid anatomy a distinctive entity. Until more exact physiologic knowledge is at hand the clinician and pathologist must content themselves with a comparison of the evidences of disease in the patient and the anomalies of thyroid design as seen in the laboratory. Accurate histories as to the time and rate of development as well as careful postoperative observations would add valuable information not found in the literature. We deprecate the use of a simple clinical sign or symptom in naming a certain thyroid disease or type. For example, it is evident in the literature as well as in our study that exophthalmia may be accidental in any hyperthyroidism and yet many clinicians still use it in a specific way. We are in sympathy with the appellations of toxic and nontoxic as introduced by Plummer and Wilson. These terms should, however, be borne out by an accurate clinical record before being applied. More careful accounting of the preoperative facts will undoubtedly lead to a closer agreement between clinical symptomatology and the subsequent studies of the morbid anatomy of the thyroid.

CONCLUSIONS

1. A simple clinicopathologic study is desirable in all thyroid diseases.

2. The incidence of so-called exophthalmic goiter (diffuse parenchymatous hyperplasia) in proportion to other types in endemic and nonendemic areas is of importance.

3. Pregnancy is a factor in precipitating thyroid unbalance. Miscarriages are frequent in proportion to the toxicity.

4. The pulse pressure in thyroid disturbances is usually high, being highest in the parenchymatous hyperplasia group. It is out of proportion to the ordinary changes in blood vessels occurring in early and middle life.

5. The basal metabolic rate is a valuable indicator of thyroid unbalance and should be employed after operative procedures as well as before.

6. More experimentation is desirable in determining the significance of adenomatosis, solitary adenoma and other pathologic changes, as well as the clinical effect of the amount removed.

7. A simple classification of the pathology of thyroids is given because a complicated classification of thyroid disease is futile and cannot lead to knowledge that lies in the field of proper experimentation.

SITUS INVERSUS VISCERUM

AN ANATOMIC STUDY *

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Situs inversus viscerum is that condition in which the normal arrangement of the viscera is reversed to form a mirror picture of the usual position. Such transposition is usually total but may in rare instances involve either the thoracic viscera or the abdominal viscera alone.

The subject has fascinated the medical profession for more than three centuries. There is a certain romantic distinction conferred on a person who differs so fundamentally in the arrangement of his anatomy from his fellow men.

HISTORY

A brief historical survey shows a case of reversed liver and spleen reported by Fabricius in 1600. Petrius Servius, in Rome, in 1643 recorded a case of transposed viscera. In 1824 the condition was recognized for the first time by a clinician. It was discovered by auscultation and percussion, recently acquired aids to clinical examination.

From this time forward the condition has been reported with increasing frequency. In 1865, Grüber reported seventy cases which he had been able to compile up to that date. Küchenmeister [1] in 1884 compiled 149 cases, only forty of which appeared before 1819. Various other writers have added to this series, notably Pic, in 1895, who brought the number up to 190. In 1906 Sorge [2] was able to compile only 194 cases. In 1912 the literature was reviewed by Karashima.[3] He stated that more than 200 cases were probably on record and many others had doubtless been recognized but not reported.

From 1912 forward I have reviewed the literature and present what I believe to be a complete bibliography of the subject from that year up to the end of 1924, thereby bringing the history of the subject to date.

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* From the department of anatomy, Columbia University College of Physicians and Surgeons.

1. Küchenmeister, G. F. H.: Die angeborne vollständige seitliche verlangrung der einglweide des Menschen, Leipzig, 1883.

2. Sorge, F. G.: Kasuistischer Beitrag zur Kenntnis des Situs viscerum inversus, Thesis, Berlin, 1906.

3. Karashima, I.: Ein Fall von Situs inversus viscerum totalis, Thesis, Munich, 1912.

The important milestones passed in the history of situs inversus are:

1. The report of the first human cases by Fabricius and Servius, 1606 and 1643.

2. The first clinical observation of the condition in 1824, using auscultation and percussion.

3. The first diagnosis of the condition by roentgenograph in 1897.

It is interesting to note the change in case reports over this long period of years. Of the seventy odd cases reported by Grüber up to 1865, only five or six had been reported in living subjects. Until 1900

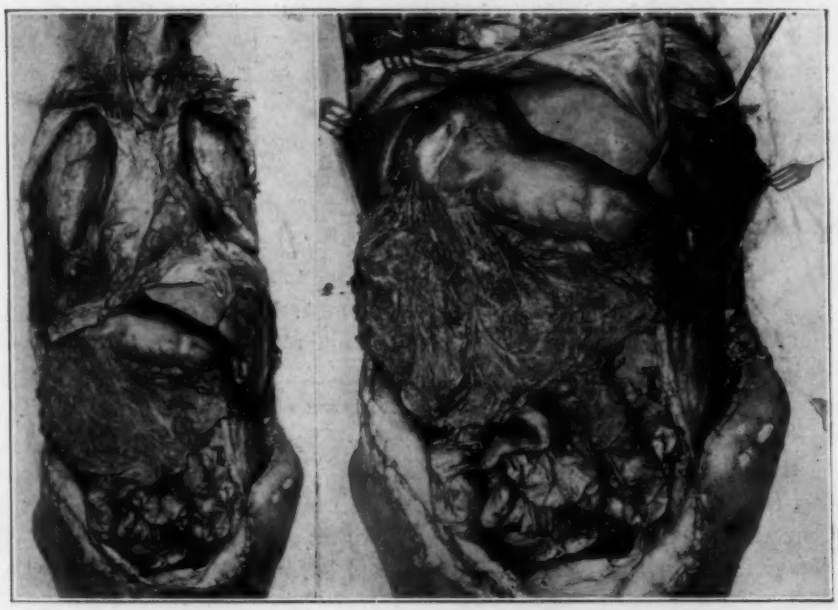

Fig. 1.—Thoracic and abdominal cavities reveal transposition of viscera: the heart lies to right in its intact pericardial sac; the liver occupies the left hypochondrium, while the greater part of the stomach lies to right of midline in right hypochondrium; the omentum overlies remaining gastro-intestinal tract, concealing its position.

the vast majority of cases were discovered post mortem or were revealed in the course of surgical exploration of the abdomen. Since that date the number of cases discovered by clinical observation has rapidly risen to a point where they form the great bulk of the case records. This is probably because of the greater frequency of routine physical examination and the wider application of roentgenology as a diagnostic procedure. More than 90 per cent of the case reports at the present time deal with the living subject.

It is not possible to determine with absolute accuracy the number of cases of situs inversus that have been reported. Many authors report

Fig. 2.—Thorax showing relation of structures in superior part of interpleural space: the retraction of the mediastinal parietal pleura on either side reveals the phrenic nerves lying between the pleura and the intact pericardium; the right innominate vein runs obliquely and to the left, in front of the three main branches of the aorta; this vein formed by the junction of the right subclavian and the right internal jugular veins joins the short left innominate trunk, 2 cm. in length, to form the left superior vena cava. The left superior cava extends downward, receiving a pericardial investment to enter the left atrium. Its extrapericardial course is 5 cm. in length and its intrapericardial course about 2.5 cm. The aortic arch covered by the fibrous pericardium is seen extending upward, backward and to the right, giving off the following branches in order from left to right: (1) the innominate, which subsequently divides into left common carotid and left subclavian arteries; (2) the right common carotid artery, and (3) the right subclavian artery. These vary in no way from the usual arrangement except for the transposition.

Fig. 3.—Open pericardial sac showing right ventricle forming apex of heart, situated about 6.25 cm. to right of midline; the left ventricle lies to front and forms greater part of left and inferior borders of heart; the left atrium has opening into it the superior vena cava and the inferior vena cava, which passes through diaphragm to left of midline. The right atrium posteriorly has the openings of the four pulmonary veins. The transverse sinus, indicated by probe, behind the arterial mesocardium is present without variation aside from the fact that its anterior boundary is the pulmonary artery on the right and the aorta on the left, owing to the transposition. The ascending aorta extends upward from the right ventricle between the superior cava on the left and the pulmonary artery on the right. The first 4 cm. of this vessel lies within the serous pericardium while the entire vessel to the arch is covered by the fibrous pericardium. The ascending aorta turns backward and to the right to form the aortic arch described above.

one or more cases and add additional cases from other clinics or from their colleagues. This leads to considerable reduplication, which must be guarded against. As far as can be determined with reasonable accuracy, since 1912 there have been recorded some 160 cases of situs inversus, which brings the number reported by Karashima at that date up to an approximate total of a little less than 400.

FREQUENCY

The condition is now generally regarded as less rare than it was formerly believed to be, but we are not convinced that it is as frequent as some writers imply.

In 1902 when Arneil [4] wrote on the subject, he communicated with nineteen prominent internists and five anatomists in an effort to compile the number of cases each had seen. Five internists and four professors of anatomy had never seen a case.

Roentgenologists are rather apt to see a larger proportion of the total number of cases than clinicians or anatomists. In response to a letter written by Upson [5] of Battle Creek to thirteen roentgenologists in 1921, the number which each stated that he had seen was rather vague. Some of them had never seen any. LeWald [6] at that time stated that he had seen twenty-two cases and in a recent report presented twenty-nine cases that he himself had observed. He admits that the frequency of twenty-nine cases in 40,000 examinations, or 1 in 1,400, is high and we are inclined to agree that his experience has been unusual.

In the anatomic laboratory of the Columbia University College of Physicians and Surgeons during a period of forty years about 10,000 subjects have been examined in routine dissection and the case presented here is definitely the first instance of complete or partial transposition of the viscera; in the years preceding 1885 we have no record of any similar case.

Sherk [7] stated in 1922 that the Mayo Clinic could find only ten cases out of 347,000 registered in the twelve year period preceding. A report of the frequency of this condition among the recruits of the various armies recently mobilized would have been extremely interesting, but in reply to a recent inquiry the Surgeon General's Office stated that there were no data available on this subject.

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4. Arneil, J. R.: Clinical Observations on Congenital and Acquired Transposition of Viscera, Am. J. M. Sc. **124**:885, 1902.

5. Upson, W. O.: A Case of Situs Inversus, J. Mich. M. Soc. **17**:362 (Sept.) 1918; Transposed Viscera, Am. J. Roentgenol. **8**:385 (July) 1921.

6. LeWald, L. T.: Complete Transposition of the Viscera, J. A. M. A. **84**: 261 (Jan. 24) 1925.

7. Sherk, H. H.: Total Transposition of Viscera, Surg., Gynec. & Obst. **35**:53 (July) 1922.

While the condition is doubtless recognized more often at the present time than formerly, we are in no position to discuss its frequency with certainty.

THE INDIVIDUAL

A great deal has been written concerning the individual possessing this unusual arrangement of the viscera. One writer stated that he has seen seven patients, all of whom were in poor health. It is at times reported that the individual with the inverted situs is left handed. Two reports were noted in which the condition existed in two brothers and

Fig. 4.—The heart lifted out of its pericardial sac with the oblique sinus of the serous pericardium exposed, extending upward to the left; the orifice is bounded below and to the left side by the inferior vena cava and above to the right by the right pulmonary veins.

one in a brother and a sister. One roentgenologist reported four cases in the same family.

The majority of case reports, however, show that the individual differs not at all from the ordinary human being. He does not seem to be left handed more frequently than his fellows. He is apt to live his life unmarked by any peculiarity and die of the same diseases that carry off the rest of mankind. There is no proof that heredity plays a part in

Fig. 5.—Termination of thoracic duct: the duct passes upward in the superior mediastinum from behind the aortic arch, behind the right subclavian artery; passing into the neck it curves outward, upward and to the right, behind the right vagus nerve, the right common carotid artery and the right internal jugular vein; it passes in front of the right subclavian artery and the vertebral artery and vein; it terminates in a bulbus enlargement that empties into the junction of the right subclavian and the right internal jugular veins, lying directly in front of the medial margin of the scalenus anterior and the phrenic nerve. The right vagus nerve is shown retracted with the thoracic duct passing upward and outward between the retractors to disappear behind the right internal jugular vein; its terminal enlargement and cardiac branches of the cervical sympathetic trunk crossing in front of the duct can readily be seen.

this condition. The European case reports usually end with the observation that the individual was quite fit for military duty.

ETIOLOGY

The theories as to etiologic factors in this condition are numerous. The following are some of the views that have been held:

1. The persistence of a right omphalomesenteric vein influencing the shifting of the stomach to the right instead of to the left.

Fig. 6.—Left vagus nerve and its recurrent branch; this branch arises in front of the left subclavian artery and winds from before backward around that vessel, ascending obliquely behind the left common carotid artery and behind the inferior thyroid artery to the groove between the trachea and the esophagus.

2. The influence of the umbilical cord. In situs inversus it is wound spirally to the right instead of to the left. The blood column flowing in the reverse direction is responsible for the turning of the heart to the

opposite side. It is difficult to understand how the blood column in the umbilical vein, after passing through the liver, could exert much force. This theory seems utterly untenable.

3. The turning of the embryo to the right side of the unbilical vessels instead of to the left as it normally lies.

The relation of situs inversus to anomalies of the abdominal veins, from the etiologic standpoint, has been studied extensively by von

Fig. 7.—Right vagus nerve and its recurrent branch; the latter nerve arises from the vagus to the right of the aortic arch and passes backward, then upward behind the arch to ascend along the side of the trachea, between it and the esophagus.

Werdt.[8] In a careful survey of a large number of case reports of situs inversus he noted the anomalies of the abdominal veins, and concluded that the embryology of the venous system afforded no constant explana-

8. Von Werdt, Felix: Zur Kenntnis des Situs inversus under der mit demselben häufig verbundenen Anomalien im Bereiche der grossen Abdominal venen, Arch. f. mikr. Anat. **95**:37, 1921.

tion of the etiology of situs inversus, because most of these variations developed after the reversed asymmetry of the viscera had been determined.

The existence of situs inversus in certain types of monsters has long been recognized. Morrill's [9] study of symmetry reversal and mirror imaging in monstrous trout, with a comparison of a human dicephalic monster, is an interesting piece of work. This author has compiled six cases of these dicephalic monsters presenting a reversed visceral asymmetry of one of the components. He states that there is a general agreement that transposition of viscera does not occur in duplicate twins. The question is raised by Morrill why mirror imaging occurs occasionally, but not always, in certain types of monsters.

Wilder's [10] investigation of duplicate twins and double monsters is interesting but not entirely satisfactory in an attempt to interpret the results in terms of etiology of transposition of viscera. This author found that double monsters show all degrees of mirror imaging but that duplicate twins presented only vestiges of such. In a small number of cases investigated he found in a majority a reversal of the index finger pattern. The pattern of the right index finger of twin A was the mirror image of the left index finger pattern of twin B. This symmetry reversal is emphasized as evidence of the single ovum origin of these individuals and interpreted as the lost trace of an earlier more general mirror imaging which has been subsequently outgrown.

Newman,[11] in his study of armadillo quadruplets, found that there was no reversal of asymmetry of the viscera but that there is a reversal of the pattern in the tegumentary system. He concludes that there is so little tendency to mirror imaging in duplicate human twins and so much in the armadillo because the human twins become isolated at a considerably earlier period than the armadillo quadruplets. He states that the earlier the separation takes place the more complete is the reorganization of symmetry relations in the separated individuals and the less is the residuum of the common mirror symmetry. Double monsters begin to separate comparatively late in ontogeny and therefore show pronounced mirror imaging.

These observations are of great interest but they fail to explain the basic cause of the situs inversus viscerum. We must pursue a more

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9. Morrill, C. U.: Symmetry Reversal and Mirror Imaging in Monstrous Trout and Comparison with Similar Conditions in Human Double Monsters, Anat. Record **16**:265, 1919.

10. Wilder, H. H.: Duplicate Twins and Double Monsters, Am. J. Anat. **3**, 1904; Morphology of Cosmobia, ibid. **8**, 1908; Palm and Sole Studies, II, Biol. Bull. **30**:135, 211, 1916.

11. Newman, H. H.: Heredity and Organic Symmetry in Armadillo Quadruplets, Biol. Bull. **30**:173, 1916.

Fig. 8.—Right pleural cavity and lung: the single primary oblique fissure is seen dividing the lung into two lobes, an upper and a lower lobe; the fissure extends from the upper and posterior part of the hilum to the costal surface, from about 5 to 6 cm. below the apex, and then continues downward and forward to the inferior border where it is situated about 4 cm. behind the anterior extremity of that border. It then extends upward to the inferior margin of the hilum. The right pleural cavity contained several hundred cubic centimeters of thick turbid pus and the diaphragmatic and costal pleurae are much thickened and covered with fibrinous plaques as is the interlobar visceral pleura, showing the suppurative pleurisy suggested in the clinical note of Dec. 13, 1921.

Fig. 9.—Left pleural cavity and lung; the pleura was shiny and glistening throughout. The arrangement of lobes and fissures is interesting: the primary oblique fissure extends from the upper part of the hilum to the costal surface at a point about 6 cm. below the apex; it extends obliquely downward and forward 7.5 cm. to a point on the lateral costal surface where it is joined by the transverse fissure; it continues its course to the inferior margin where it terminates 7 cm. below and behind the anterior extremity of that border. The transverse fissure commences on the anterior margin 6.5 cm. above its lower extremity and runs upward and outward to intersect the oblique fissure and is then carried laterally, incompletely subdividing the inferior lobe into a superior and inferior portion. This approaches the frequently recorded variation of four lobes in the right lung. In this case the left lung shows three complete lobes and a fourth incomplete at the expense of the inferior lobe. The two additional grooves shown at the lower part of the inferior lobe are merely impressions that do not in any sense approach the semblance of fissure. The vena azygos, receiving the left superior intercostal vein, arches over the root of this lung.

fundamental search in any effort to determine the causes of this condition.

Zurstrassen [12] observed, in his studies of *Ascaris megalocephalus,* that in the eight cell stage one egg out of every thirty or forty showed the inverted situs and that four of 125 adults similarly presented reversed asymmetry of the viscera. He decided that the asymmetry of the embryo present in the eight cell stage was probably responsible for the adult situs inversus.

Fig. 10.—Detailed view of left upper quadrant of abdomen or left hypochondrium: the liver, of normal size, is divided into a large left and a smaller right lobe by the sulcus into which passes the falciform ligament with the obliterated umbilical vein in its free margin. Beneath the left lobe of the liver lies the gallbladder and from the porta hepatis passes the lesser or gastrohepatic omentum, downward and to the right to the lesser curvature, or left border, of the stomach, the epiploic foramen of Winslow is seen behind the left extremity of the lesser omentum.

Crampton [13] showed among certain gasteropods a correlation between the position of the organs and the segmentation pattern. The usual type of asymmetry with a dextral shell is associated with a spiral cleavage

12. Zurstrassen, O. L.: Embryonal Entwickelung der Ascaris Megalocephalus, Arch. f. Entwçkingsmechn. d. Organ **3**:27, 1896.

13. Crampton, H. E.: Reversal of Cleavage in a Sinistral Gasteropod, Ann. New York Acad. Sc. **8**:167, 1894.

to the right. Other forms such as Physa, however, have a sinistral shell with reversed asymmetry of the viscera and a reversal of cleavage. The first evidence of variation appeared at a late two cell stage.

There are some observations that suggest that in the vertebrates also the factors for reversed asymmetry may be present in early developmental stages.

Perhaps the most interesting investigations on the subject dealing with vertebrate material are those of Spemann [14] and later of Pressler,[15] working with *Bombinator igneus* and *Rana esculenta* during the neurula stage, they excised a square of the medullary plate with a portion of the primitive foregut and rotated it 180 degrees so that the original cephalic end was placed caudad. A number of these embryos developed with a complete situs inversus.

Levy,[16] working with *Triton taeniatus,* tried to rotate the heart anlage in a like manner to produce situs inversus but failed because he was unable to isolate it.

The question of what determines the normal asymmetry must be solved before we are in a position to attack the problem of etiology of *reserved* asymmetry of the viscera. From the investigations quoted it seems probable that such asymmetry is not primarily the result of local variation but is due to factors operating at an early ontogenetic period.

We are still in doubt regarding the etiology of this condition, with a number of interesting lines of investigation suggested.

The case presented here was discovered in the dissecting room. In subsequently tracing the body it was found that the condition had been recognized and studied by the clinicians in a hospital of this city, so we are fortunately able to present a rather complete history. The condition is a complete transposition with a variation in the genito-urinary tract, a fused kidney situated entirely in the left umbilical and lumbar regions. The two components of this double organ are easily recognized and the ureters pursue a relatively normal course after passing over the pelvic brim.

REPORT OF CASE

C. T., a man, aged 24, born in Italy, was admitted Nov. 25, 1921, and died Jan. 3, 1922. The final diagnosis was bronchopneumonia, nephroptosis and transposition of the viscera. The chief complaint was that he had had indigestion for eight months.

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14. Spemann, H.: Ueber eine neue methode der Embryonal's Transplantation, Verhandl. d. deutsch. Zool. Gesellsch, 1906; Ueber Embryonale Transplantation, Verhandl. d. Gesellsch. deutsch. Naturf. u. Aerzte, 1906.

15. Pressler, K.: Beobachtungen und Versuche über den Normalen und inversen situs viscerum et cordis bei Anurenlarven, Arch. f. Entwcklngsmechn. d. Organ. **32**:1, 1911.

16. Levy, Oskar: Entwicklungsmechanische Studien am Embryo von Triton Taeniatus, Arch. f. Entwcklngsmechn. **20**:335, 1906.

The patient had been well until the onset of the present illness. The past history was negative aside from chancre three years before. After each meal he had distress and an uncomfortable feeling in the epigastrium and gaseous eructations. He had no pain and did not vomit. He had lost weight, and came to the hospital because of acute indigestion.

Physical examination showed a poorly nourished adult, not acutely ill. The eyes and ears were normal, and the mouth, aside from bad teeth. There was

Fig. 11.—Mesenteric root with the ascending and transverse colons retracted, extending from duodenojejunal junction at level of second lumbar vertebra to right of midline, downward to left iliac fossa where terminal ileum is seen emptying into cecum from right to left.

asymmetry of the ribs. Chondrosternal junction did not correspond on the two sides. There was retraction of the supraclavicular and the infraclavicular spaces. Expansion was normal, equal and symmetrical. The lungs were resonant throughout. Breath sounds were normal. The voice and tactile fremitus were normal. No râles were heard.

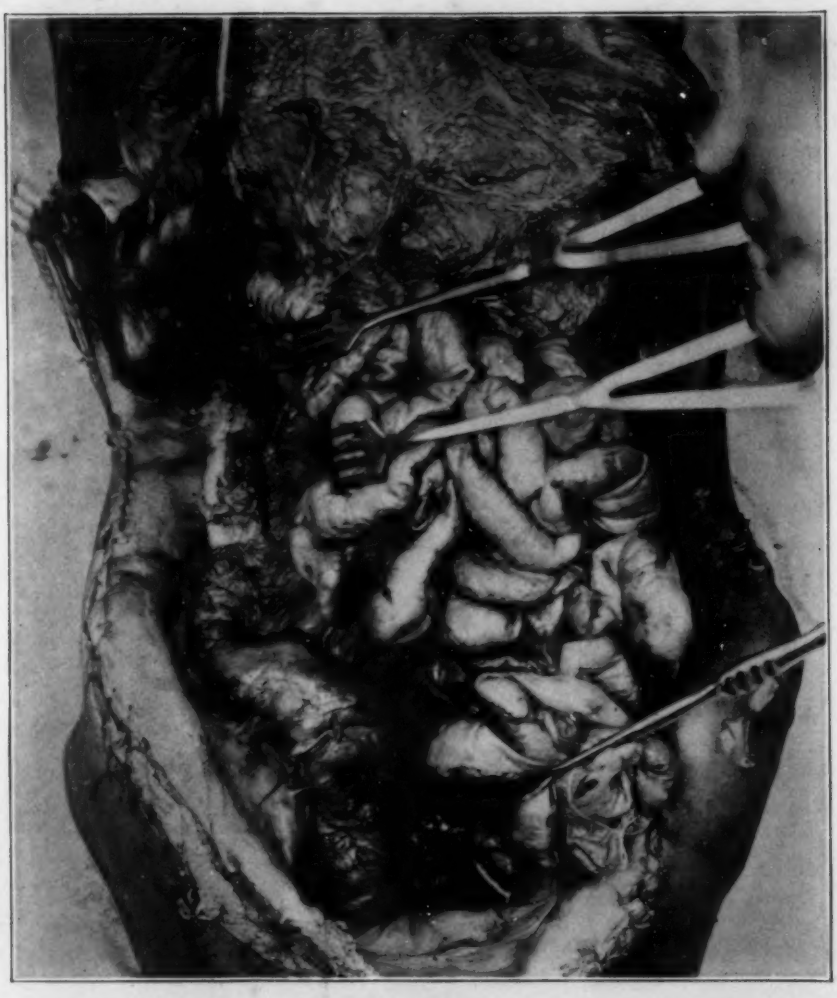

Fig. 12.—Spleen occupying right upper quadrant or right hypochondrium lying below dome of diaphragm on tenth, eleventh and twelfth ribs. The spleen is in all respects normal, presenting a large gastric surface which supports the right extremity of the posterior surface of the stomach. The splenic flexure of the colon is just visible below the spleen; the descending colon is seen extending through the right lumbar region to the iliac fossa where it becomes the iliac colon. The sigmoid colon, shown in part, is not much over 20 cm. in length and has a relatively short mesocolon; it passes into the rectum from right to left. The right lumbar region with the small bowel retracted reveals no evidence of a right kidney.

In the right fifth interspace the apex was felt 7 cm. to the right of the midline. The first sound at the apex was of good quality and regular in force and rhythm. There were no murmurs. The pulmonic second sound was greater than the aortic second. The pulse was regular in force and rhythm. The systolic blood pressure was 112, the diastolic 70. The arterial walls were not palpable.

The liver was on the left side, the upper border at the fifth rib; the lower border was not felt. The stomach percussed in the right side; the spleen and the right kidney were not felt. In the left lower quadrant, in the region of the kidney, there was a mass that resembled kidney in size and position; it was movable like a floating kidney, very tender, irregular in outline, nodular and did not move with respiration. The abdominal walls were lax. The extremities were negative. Reflexes were diminished. The right testis was lower than the left.

The provisional diagnosis was congenital transposition of the viscera; floating kidney; neoplasm of the left kidney, and neoplasm of the gastro-intestinal tract.

Heart Measurements in Centimeters

Intercostal Space	Right Midsternal Line, Cm.	Left Midsternal Line, Cm.
2	4	2
3	6.5	3
4	6.5	4
5	7.5	

Roentgenograms could not be obtained, but the reports are submitted as follows:

November 29, there was noted complete transposition of the viscera; examination of the chest showed moderate emphysema. November 30, examination of the genito-urinary tract revealed no calculus in either ureter. There was some enlargement of the right kidney, and it was moderately ptosed.

November 30, fluoroscopic examination showed the position of the heart to be entirely transposed. The cardiac axis had normal curves, the normal left curves on the right and the normal right curves on the left. No examination of the inner cardiac curves was made. The shape was normal, and there was no definite enlargement. The aorta was normal. The measurements were: maximum transverse, 11.5 cm.; total length, 13.5 cm.; angle of inclination, 41 degrees; broad diameter, 8.9 cm.; width of aorta, second rib, 4.1 cm., and width of pulmonic field, 26 cm.

December 2, examination of the gastro-intestinal tract showed complete transposition of the viscera. The stomach was on the right side of the abdomen. There was no defect in the gastric outline. The bulbus duodeni was filled with difficulty but completely. No gastric retention was noted at the end of six hours. The head of the column was in the cecum, the tail in the ileum. A twenty-four hour examination showed the head of the column in the rectum, the tail in the cecum; haustration was deep and regular; the appendix was visualized 1 inch (2.5 cm.) long, extending inward, and was not tender. There was transposition of the gastric and the gastrocolonic mass in the lower quadrant.

December 6, a cystoscope passed without difficulty. The bladder was emptied of 9 cc. of pale amber urine. The ureteral orifices were normal in position and in appearance, the openings being very small. The bladder texture was normal throughout. Both ureters were catheterized, pale, amber urine being obtained on the left side and a smaller quantity, slightly blood tinged, returned from the right. Six milligrams of phenolsulphonphthalein intravenously injected appeared on each side in three minutes. The specimen was colored for ten minutes. A double pyelogram was made.

A mass in the left upper quadrant just lateral to and above the umbilicus was quite freely movable, shaped like a kidney and rather painful on pressure. No kidney pain was felt in the loins. There were no urinary symptoms and no hematuria. The impression was that the left kidney was movable, and that there was transposition of the viscera.

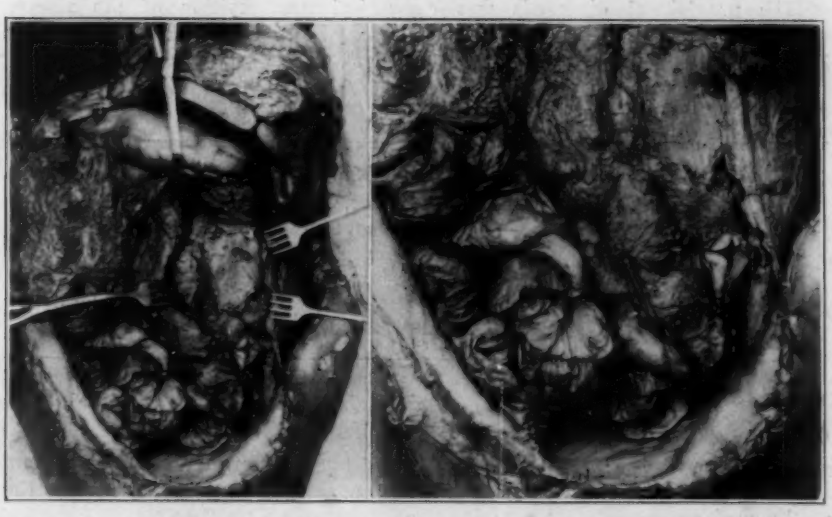

Fig. 13.—The left iliac fossa revealed the cecum with an appendix a little above and behind in the retrocolic position; the appendix grossly was quite normal. Above and behind the appendix and the ascending colon was a large dense mass measuring about 10 cm. in diameter, adherent to the overlying viscera and underlying iliac fossa by dense scar tissue; lying directly beneath the abdominal operative wound, this mass had evidently been the objective of the exploratory operation described in the clinical record of this patient.

The pyelogram showed an opaque catheter present in the left ureter, extending upward and outward from the level of the third sacral segment to a point about 1 cm. above the iliac crest and 7.5 cm. from the midline. The tip of the catheter entered the pelvis from the outer side. There was marked distortion of the pelvis and the calices. The pelvis was divided into upper and lower arms from the extremities of which spring the minor calices.

December 13, at operation a vertical incision 6 cm. long was made through the left rectus abdominis. The ascending colon was found misplaced inward and the omentum was adherent to the large mass under the colon and to its outer side. The posterior peritoneum was opened exposing this mass and revealing a fused kidney with the right kidney calices pointing to the left

Fig. 14.—The dissection exposing the genito-urinary system was difficult because of the dense scar tissue resulting from the operative procedure and the inflammatory process before and after. The dissection was done retroperitoneally, an attempt being made to preserve carefully the overlying peritoneal structures intact. The renal mass, or fused kidney, consisting of two apposed kidneys each with its own ureter, is shown; the entire lobulated mass measured about 12 cm. in longitudinal and transverse diameter and 4.5 cm. in anteroposterior diameter and was situated in the left iliac fossa, extending from a little to the right of the midline to within 3 cm. of the iliac crest. The right kidney was closely imposed on the left, occupying the right superior aspect of the fused mass with its hilum in front and to the left. The left kidney, somewhat larger, occupied the left and inferior aspect of the mass with its hilum to the left and in front. The right ureter springs from three major calices at the hilum of the right kidney, lying in front of the right renal vein and artery. Commencing at the midline of the body, it passes downward and to the right over the body of the fifth lumbar vertebra, directly in front of the right iliac vein, and over the pelvic brim, down the right lateral pelvic wall to terminate at its usual site. The left ureter springs from four major calices at the hilum of the left kidney, lying to the outer side of the left iliac fossa. The ureter is ventral to the various vascular structures that enter or leave the hilum. It passes over the inferior pole of the left kidney, crosses the external iliac vessels, passing over the pelvic brim down the left lateral wall of the pelvis, is crossed by the ductus deferens, and terminates also at its usual site.

Fig. 15.—Vascular pedicle of fused renal mass showing inferior vena cava, abdominal aorta and various renal vessels; the inferior cava is seen lying to the left of the vertebral column formed by the confluence of the right and the left iliac veins; the abdominal aorta, bifurcating at the level of the body of the third lumbar vertebra and its two terminal iliac branches, is seen to the right of the cava. The following arrangement of the vascular structures of the renal mass is to be noted:

Veins: From the left kidney there emerges (*a*) a rather large vein from the hilum passing over the lower pole to empty into the left internal iliac or hypogastric vein, shown as the lower vessel in the illustration; (*b*) a large, short, thick trunk which empties directly into the inferior vena cava; the torn vein and its orifice into the vena cava can be seen; (*c*) from the lower pole of the right kidney, a vein passes upward and to the right of the fused renal mass to join with a large vein formed by two tributaries from the ventral aspect of the upper poles of both right and left kidneys. This trunk after receiving two or three lumbar veins passes behind the aorta at its bifurcation on the body of the third lumbar vein and empties into the inferior vena cava.

Arteries: (*a*) the abdominal aorta just before its bifurcation gives off a large renal artery that goes to the upper pole of the renal mass giving branches that end at the hilum of each kidney; (*b*) the left iliac artery sends a good sized branch to the dorsal aspect of the left kidney; this divides into two large branches which eventually reach the hilum, one, the posterior aspect, and the other, the anterior aspect, passing over the upper pole on the way; (*c*) the right iliac artery sends a small, short, thick trunk to the lower pole and hilum of the right kidney.

and the kidney body lying over the lumbar vertebrae. To this was attached the left kidney, about twice the size of the right and extending to the left with its calices pointing to the right. The body of the left kidney was readily freed. Three vascular pedicles were found, the first under the hilum, behind the pelvis, the vessels arising at the level of the fourth and the fifth lumbar vertebrae. The third vascular pedicle descended from about the second to the third lumbar vertebra between the fused convex borders of the kidneys. In this pedicle the vein lay in front of the artery.

Focal suppuration was found in the lower pole of the left kidney. The kidney parenchyma and the pelvis were carefully explored for tuberculosis and tumor. A cigaret drain was inserted down to the point of focal suppuration.

December 13, in the right axillary space there was dulness, increased voice and diminished fremitus. Subcrepitant râles were heard in the anterior axillary line. In the posterior axillary line breathing was bronchial though slightly distant. The impression was that the patient had pneumonia with extension to the pleura. Thoracotomy was advised if the temperature continued to fluctuate.

The patient died, Jan. 3, 1922, three weeks after the operation, death being due to sepsis, with localization of suppuration in the fused kidney and a large collection of pus in the right pleura.

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THE MECHANISM OF LOCALIZATION OF GAS IN THE PLEURAL CAVITY AND ITS CLINICAL APPLICATION IN PNEUMOTHORAX THERAPY*

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Thoracoplasty has rightly been considered as a further development of artificial pneumothorax in the surgical treatment of pulmonary tuberculosis, the prime purpose of each being to put the diseased lung at rest. However, in the light of our newer understanding of the localization of gas in the pleural cavity with relation to the diseased and nondiseased portion of the treated lung, thoracoplasty cannot be considered to parallel artificial pneumothorax in its mode of action and ultimate effect. In one class of cases at least the action of artificial pneumothorax, if administered in the proper way, is unparalleled by any other method; it enables the complete compression of the diseased portion without affecting the functioning portion of the treated lung. It is best accomplished in persons with a soft lesion of the exudative type of pulmonary tuberculosis limited to one area of the lungs which is more or less free from pleural adhesions.

This gas distribution in the pleural cavity is based on definite biophysical laws and principles of pneumodynamics and should be made use of in every case treated with artificial pneumothorax. A clearer understanding of these pneumodynamic principles would probably lead to a wider application of artificial pneumothorax in early cases of pulmonary tuberculosis before the lesion becomes far advanced, when this therapy, as well as thoracoplasty, is but an ameliorative measure.

MECHANISM OF GAS LOCALIZATION IN PLEURAL CAVITY

The elastic tissue of the lung, like any other elastic substance, possesses both an expansile and a contractile force. Both these forces come into play in the physiologically functioning lung, which is kept expanded in the air tight pleural cavity by virtue of the difference between its intrapleural and intrapulmonary pressures to which it is subjected. The intrapulmonary surface is exposed directly to the atmospheric pressure through its air passages, whereas the rigid wall of the thorax transmits only very little, if any, of the atmospheric pressure to its pleural surface, and the easily distensible alveoli yield therefore to the atmospheric pressure, putting the entire lung on a stretch. The

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* From the Jewish Consumptives' Relief Society Sanatorium.

intrapleural pressure is therefore equal to the atmospheric pressure minus the tension of the expanded lung.

Any force that increases the intrapleural pressure curtails the expansion of the lung, this curtailment being directly proportional to the difference between the intrapleural and intrapulmonary pressures. Air introduced into the pleural cavity naturally increases the intrapleural pressure, but as long as this pressure is below that of the intrapulmonary, the expansibility of the lung will assert itself with each inspiration. When the intrapleural and the intrapulmonary pressures are equalized, both the contractility and expansibility of the lung tissue are in a state of equilibrium.

In my article on the classification of artificial pneumothorax and the clinical value of the several types [1] I discussed in detail how pathologic processes may diminish either the expansibility alone or the contractility alone, or both of these properties might be lost at the same time. In atelectasis the expansile force of the pulmonary tissue is reduced, and the contractile force is present. In hypertrophic emphysema the expansibility is present but the contractility is diminished. In caseous areas of the lung both the expansile and contractile properties are lost entire; consequently such tissue will yield easily to any external pressure to which it might be subjected. Fibrous tissue possesses intrinsic contractile power to some degree, but it is very resistant to external forces. However, once compressed it will never tend to reexpand. A tuberculous lung almost always exhibits all these pathologic processes in various proportions.

When a small amount of air is introduced into the pleural cavity containing a tuberculous lung free from adhesions it will distribute itself according to the degree of resistance offered to it by the various portions of the involved pulmonary tissue. The caseous soft areas are the first to cave in, the edematous and slightly infiltrated tissues follow, whereas the uninvolved elastic lung tissue expands fully with each inspiration and displaces the introduced gas into the area left by the compressed inexpansible diseased portion. Since the upper lobe is affected in the great majority of cases of pulmonary tuberculosis, an erroneous impression was gained by some that gas introduced into the pleural cavity will always compress the apex first. Such, however, is not the case. Due to these biophysical laws of pneumodynamics just explained, gas injected in small amounts will as a rule localize over the diseased pulmonary area, no matter where it be situated, apex, middle portion or base, provided no pleural synechiae are present. The figures illustrate these views clearly.

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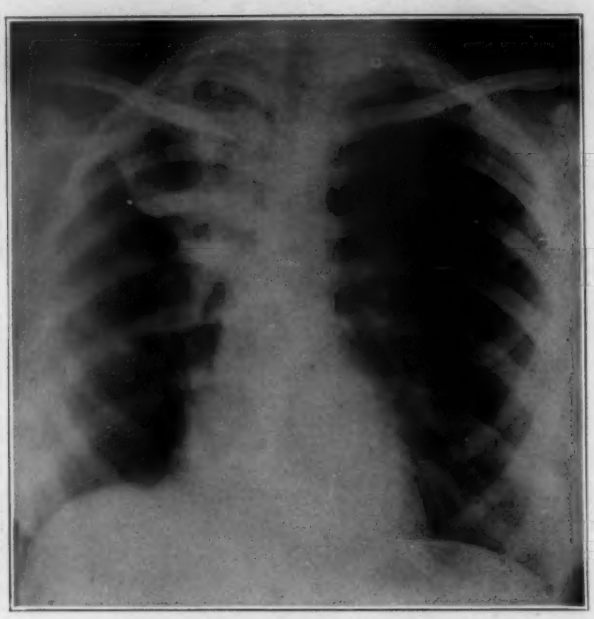

Fig. 1.—Chest showing infiltration and cavitation of right upper lobes.

Fig. 2.—Patient shown in figure 1 twenty-four hours after the introduction of 300 cc. of air into the right pleura; the localization of air over the upper diseased area should be noted.

Fig. 3.—Chest of patient shown in figure 1 in inspiration nine days after initiation of pneumothorax; the diseased upper portion is compressed, and the lower functioning portion expands and contracts with the respiratory phases.

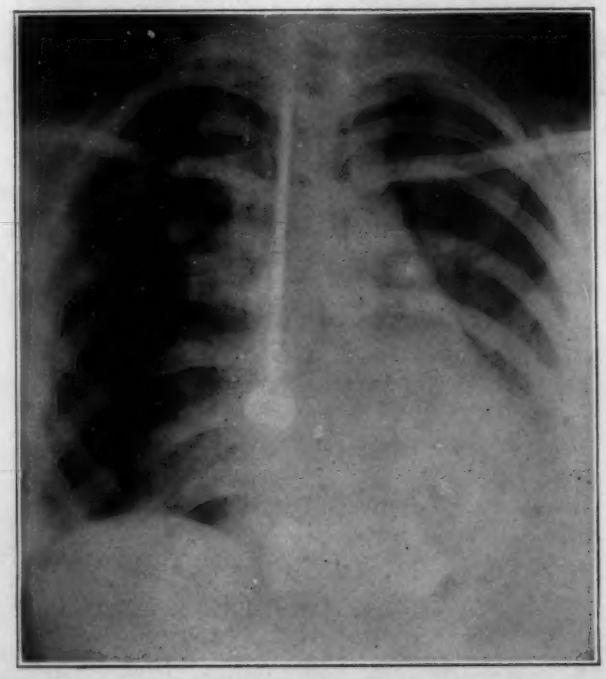

Fig. 4.—Chest of patient shown in figure 1 in expiration nine days after initiation of pneumothorax.

Figure 1 is a roentgenogram of pulmonary tuberculosis in which the lesion appears limited to the upper third of the right lung. There is a small cavity in the upper lobe surrounded with soft caseous areas, probably of the exudative type of lesion. Figure 2 is a roentgenogram of the same chest taken a few hours after the introduction of 300 cc. of air into the right hemothorax. The gas has localized itself over the upper diseased area whereas the lower functioning portion of the lung was not affected at all, expanding to its full capacity during inspiration. Figures 3 and 4 are roentgenograms in inspiration and expiration, respectively, taken nine days after the initiation of pneumothorax,

Fig. 5.—Chest showing a confluent caseous area at left base; scattered infiltration in both upper lobes.

during which time two more refills were given, each consisting of 300 cc. Altogether 900 cc. was administered. The intrapleural pressures at this time were —60 — 20 water manometer. The inspiratory roentgenogram shows that the introduced air has localized itself mostly over the diseased area, reducing it, as well as the cavity, to more than one-half its original size, whereas the unaffected portion of the lung still expands with each inspiration to almost its full capacity, leaving only a narrow slit of pneumothorax at the outer zone. During deep expiration, however, when the volume of the thorax is reduced a great deal in all its diameters, the introduced air could not room itself in the upper part alone, and it naturally distributed itself downward, compressing also the functioning portion of the lung, driving out its residual air,

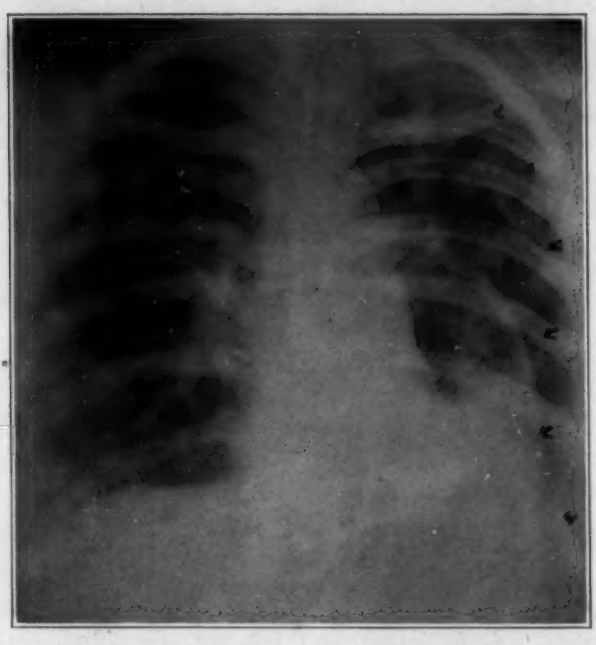

Fig. 6.—Patient shown in figure 5 in inspiration twenty-four hours after introduction of 300 cc. of air; the compressed diseased basal area and functioning upper portion of the left lung should be noted.

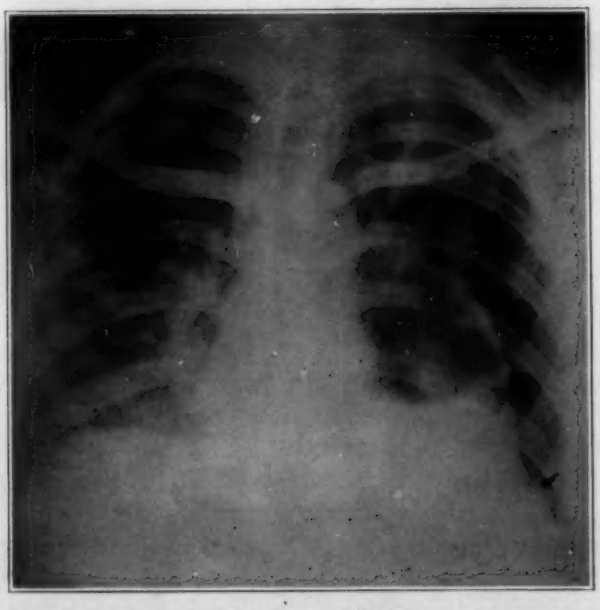

Fig. 7.—Patient shown in figure 5 in expiration twenty-four hours after introduction of 300 cc. of air.

which brings about a better ventilation of the lung, as will be discussed later.

Figures 5, 6, 7 and 8 illustrate the same pneumodynamic principles, though here the lesion is at the base. Figure 5, a roentgenogram taken one day before pneumothorax was initiated, shows a dense confluent shadow involving the entire lower third of the left lung. This was interpreted as a soft basal lesion. Three hundred and fifty cubic centimeters of air was introduced and roentgenograms, both inspiratory and

Fig. 8.—Patient shown in figure 5 three months after initiation of pneumothorax; the gas localized mostly over the diseased basal portion, compressing it completely; the upper functioning portion expands with each inspiration.

expiratory, were taken a few hours later. The air is seen to be localized mostly over the diseased basal area, the size of which changes little with the respiratory phases, whereas the upper functioning portion of the lung expands and contracts with each inspiration and expiration. Figure 8 is a roentgenogram taken about three months after the commencement of pneumothorax therapy, and shows the lower diseased portion compressed almost completely, while the upper unaffected portion is expanded almost fully during inspiration.

Figures 9, 10 and 11 bring out the fact clearly that when the lesion is disseminated throughout and affects the entire lung there can be no localization of gas over one area, but the introduced gas distributes itself equally from apex to base, provided there are no adhesions. The prepneumothorax roentgenogram shows a marked infiltration of the entire left lung. The roentgenograms taken a few hours after the introduction of 300 cc. of air show the air to be distributed equally from apex to base, and there is no appreciable change in the extent of

Fig. 9.—Chest showing dense infiltrations of entire left lung.

the collapse in either inspiration or expiration, because in this case the entire lung lost a great deal of its expansile property.

The expansibility of the lung tissue asserts itself only as long as the intrapleural pressure remains lower than the atmospheric pressure, but as soon as the intrathoracic pressure approaches that of the intrapulmonary pressure, the expansile force of the lung is put, as it were, in a state of equilibrium. Consequently, when the intrapleural pressure becomes higher than the intrapulmonary pressure it will not only inhibit the expansibility of the lung, but it also actively compresses it, the degree of compression bearing a direct relation to the increase in positive intrapleural pressures. The localization of the gas in such cases is governed by different dynamic laws, as will be indicated subsequently.

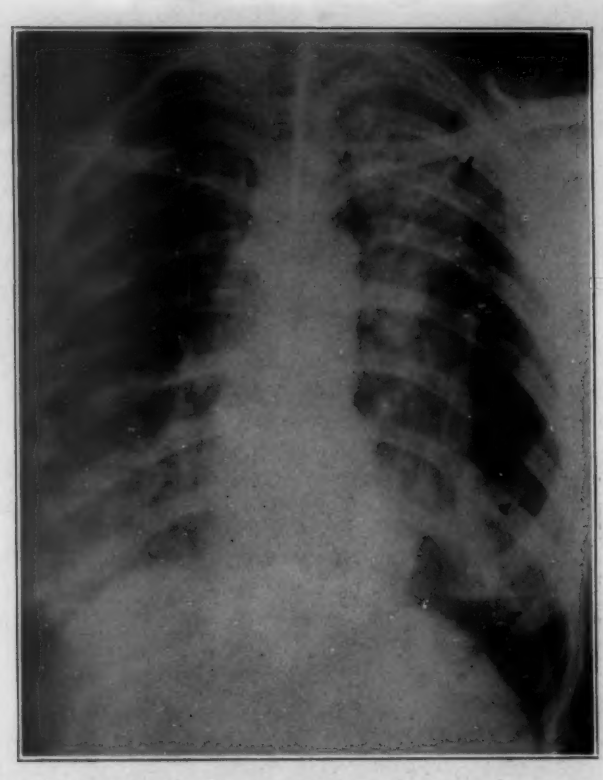

Fig. 10.—Patient shown in figure 9 in inspiration twenty-four hours after introduction of 300 cc. of air.

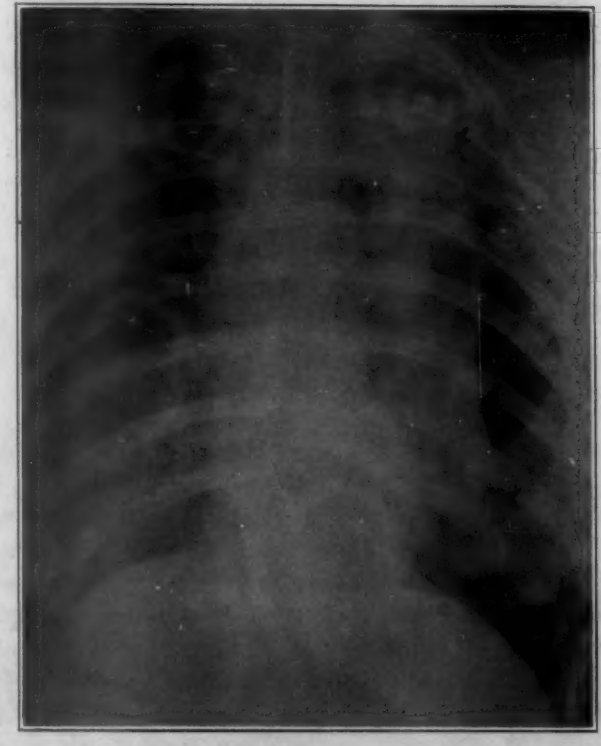

Fig. 11.—Patient shown in figure 9 in expiration twenty-four hours after introduction of 300 cc. of air; the even distribution of gas in the left pleura without change in inspiration or expiration should be noted.

EFFECT OF HIGH INTRAPLEURAL PRESSURES ON PATHOLOGIC AND ANATOMIC LUNG TISSUE

The difference in consistency between pathologic and normal anatomic lung tissue is another fundamental principle influencing the localization of gas in the pleural cavity. Soft and edematous lung tissue contains little air, and it requires but little compression to render such tissue entirely airless, reducing it to a solid mass, until it reaches the limit beyond which it cannot be compressed any more. The volume

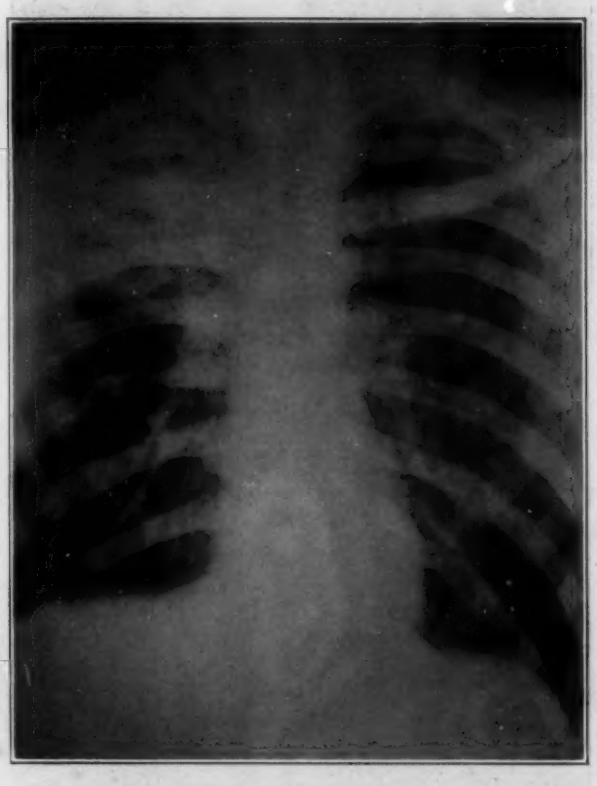

Fig. 12.—Confluent infiltration and cavitation of upper third of right lung.

of functioning lung tissue, like a sponge, consists of a great deal of air enclosed in its alveoli, and therefore when it is rendered into an airless and solid mass by high intrapleural pressure, it is reduced to a much smaller volume than diseased tissue would be under the same force of compression. This is why the older observers of pneumothorax thought erroneously that healthy lung tissue becomes more easily compressed than diseased tissue, because they administered large amounts of air, creating a positive intrapleural pressure, often as high as + 60 + 40 mercury. Figures 12, 13 and 14 serve as a clear cut illustration in this respect.

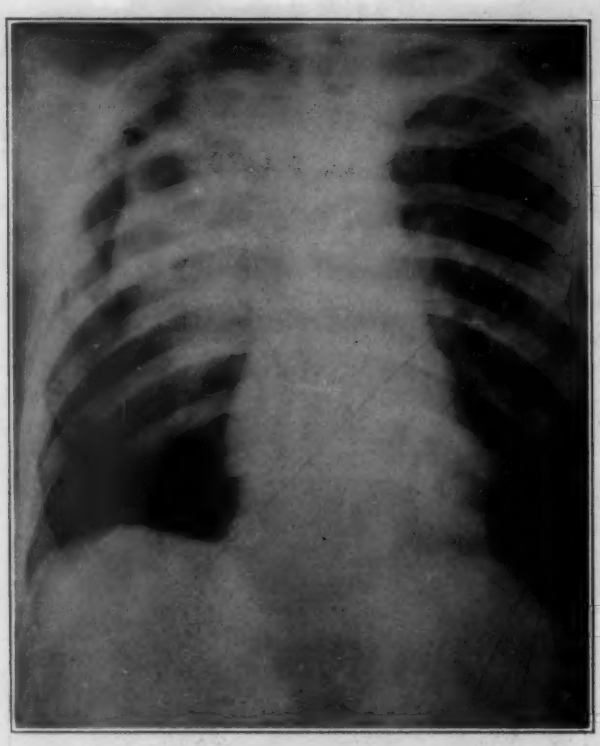

Fig. 13.—Patient shown in figure 12 after development of right spontaneous pneumothorax; intrapleural pressures at this time were + 30 + 70 mm. water manometer; the lower nondiseased portion of the lung has been reduced to a lesser volume than the upper diseased portion.

Fig. 14.—Patient shown in figures 12 and 13 twenty-one days after the spontaneous pneumothorax; intrapleural pressures were —60 —30 mm. water manometer; there is reexpansion of the lower functioning portion of the lung.

The prepneumothorax roentgenogram is shown in figure 12, revealing a massive confluent infiltration of the upper third of the right lung. If a small amount of air were introduced into this pleural cavity, leaving the intrapleural pressures negative, it should have localized itself over the diseased area, according to the pneumodynamic principles explained previously. However, the diseased portion would soon reach its limit of compressibility, and if a larger amount of air were administered, it would naturally affect the nondiseased portion of the lung, com-

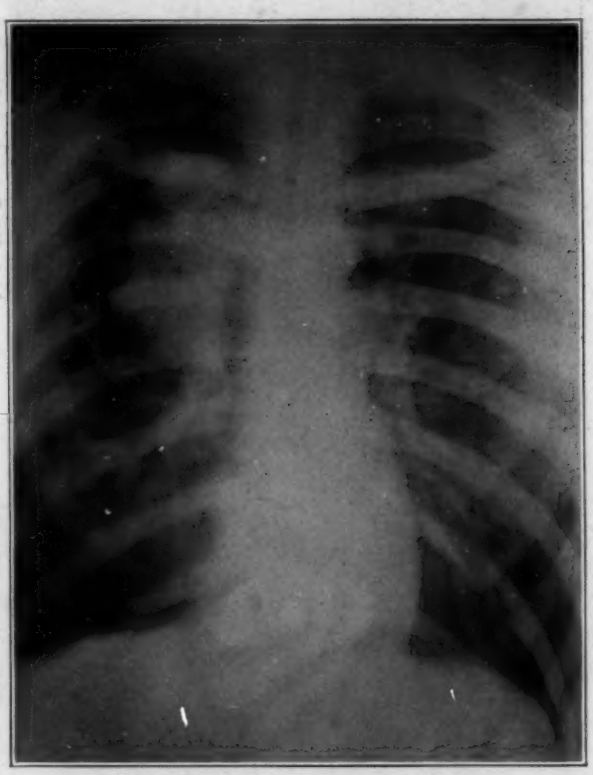

Fig. 15.—Patient shown in figures 12, 13 and 14 in inspiration three months later; the upper diseased portion, which is markedly compressed, and the lower functioning portion, which expands to almost full capacity with the respiratory phases, should be noted.

pressing it more the higher the intrapleural pressure created. Figure 13 exemplifies this view. It is a roentgenogram of the same patient as shown in figure 12, taken twenty-four hours after the development of spontaneous pneumothorax. The intrapleural pressures at this time were + 30 + 70 mm. water manometer. The lower nondiseased portion of the lung has been reduced to a lesser volume than the upper diseased portion of the lung. Twenty-one days later another roentgenogram was

taken (fig. 14) which shows a complete reexpansion of the lower unaffected portion of the lung. The intrapleural pressures at this time were — 60 — 30 mm. water manometer. Since then he has been given refills in the amounts of 400 to 500 cc., leaving the intrapleural pressures always negative. Figures 15 and 16 are roentgenograms of the same patient taken three months later in inspiration and expiration, respectively. The upper diseased portion is markedly compressed, showing

Fig. 16.—Patient shown in figures 12, 13 and 14 in expiration three months later.

little changes with the respiratory phases, whereas the lower nondiseased portion of the lung expands and contracts fully with each inspiration and expiration.

INSUFFLATED AMOUNTS WITH RELATION TO DISEASED AND NONDISEASED PORTION OF LUNG

Barlow and Kramer,[2] in a remarkable contribution on artificial pneumothorax, have drawn attention to the fact that gas introduced into the pleural cavity will tend to localize over the diseased portion of the lung, and they called this phenomenon "selective collapse." However, it is

2. Barlow, N., and Kramer, D.: Selective Collapse Under Partial Pneumothorax, Am. Rev. Tuberc. **6**:75 (April) 1922.

obvious enough that the name is only apt to mislead; the gas has no predilection for the diseased tissue but distributes itself according to the existing pneumodynamics. It is the *expansile portion* of the treated lung that is more resisting to low pressures by virtue of the atmospheric pressure to which its intrapulmonary surface is subjected, and this expansile portion drives and keeps the gas over the diseased area. But when the amount of air introduced into the pleural cavity is too large to be contained in the space left by the contracted diseased portion,

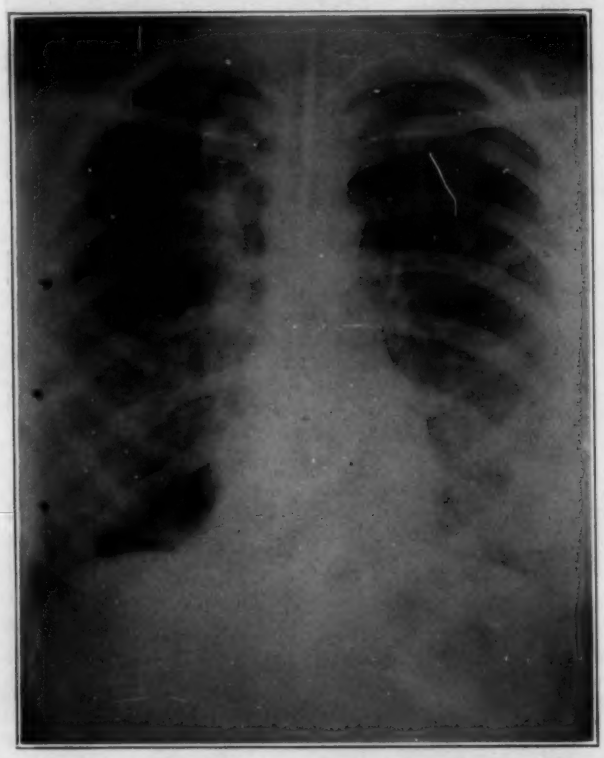

Fig. 17.—Patient shown in figure 1 five months after initiation of pneumothorax; 400 cc. were inflated at this time; there are compression and complete obliteration of cavity of upper lobe, and the lower functioning portion expands to its full capacity pushing its way into space left by the compressed area.

it will naturally encroach also on the functioning portion, and the greater the amounts of gas administered the more will this expansile portion be limited in its function.

Only careful and frequent roentgenoscopic observations will give one a fair idea of the amount to be inflated in order to keep the diseased portion compressed without affecting the functioning portion to a great extent. Figure 17 is a roentgenogram of the same patient as shown in figure 1, taken five months after the initiation of pneumothorax. The amount of air given at the last refill was 400 cc., and the intrapleural

pressures were —80 — 30 mm. water manometer. From the roentgenogram one can observe that the 400 cc. has occupied wholly the space left by the contracted diseased portion, leaving the lower functioning portion of the lung almost unaffected. At the next reinflation 900 cc. was given, and the effect on the functioning portion of the lung is clearly noticeable in figures 18 and 19. The expansile portion of the lung has been reduced to more than half its size during inspiration and to almost its minimum during expiration, whereas the contracted diseased portion has not been affected at all by this large amount of air

Fig. 18.—Patient shown in figure 17 in inspiration after the inflation of 900 cc.

and high intrapleural pressure. In other words, 400 cc. was enough to keep the diseased part at rest without affecting the nondiseased portion of the same lung; each 100 cc. exceeding these 400 was of no apparent therapeutic value, but curtailed the function of the expansile portion and thereby decreased the vital capacity of the patient, which in turn brought on dyspnea.

Obviously, it is the relation of the insufflatory amounts to the extent of the functioning portion of the lung that determines the localization of the gas. Any undue increase in the amounts inflated fetters also the function of the expansile portion; the greater this functioning portion is the smaller are the amounts to be administered, and vice versa.

Furthermore, in measuring the intrapleural pressures at various levels, I found it much higher over the compressed diseased portion than the expansile portion, in the inspiratory phase only. This means that the functioning portion of the treated lung expanding fully during inspiration leaves the pleural pressure almost at its physiologic negativity, whereas the small amount of air caused to accumulate over the

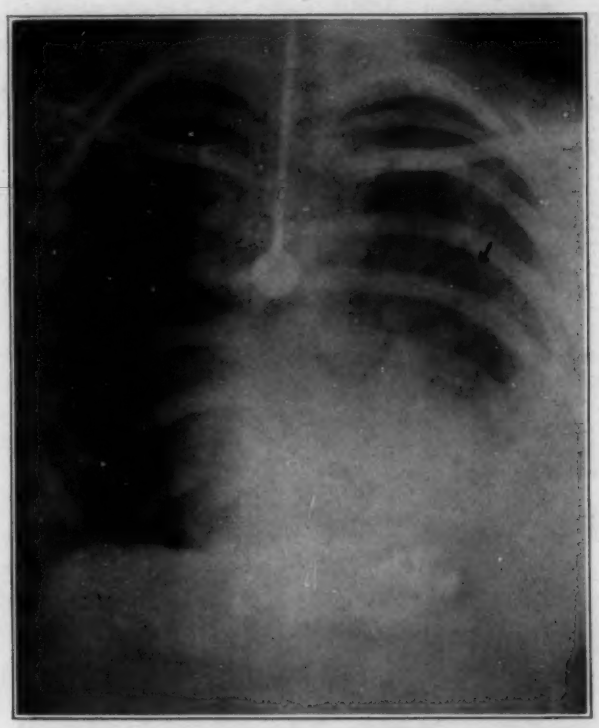

Fig. 19.—Patient shown in figure 17 in expiration after the inflation of 900 cc. In figures 18 and 19 the reduction of the lower functioning portion to half its size during inspiration and to the minimum during expiration should be noted; the compressed diseased portion was not affected at all; there was marked displacement of the mediastinum.

diseased portion increases the intrapleural pressure at that area. Only by small insufflatory amounts given at frequent intervals can this phenomenon be demonstrated.

CIRCULATORY CHANGES AND COMPENSATORY EMPHYSEMA

The various circulatory changes resulting from the deflation of one lung and the value of observing these changes in regulating the intervals and amounts of gas to be inflated into the pleural cavity, as well as their significance in the prognostication of the case treated, has been

discussed in another article.[3] However, I want to emphasize here that the compensatory ability of the right ventricle assists a great deal in keeping the functioning portion expanded and in the production of compensatory emphysema also in the contralateral lung.

The sharp distinction between compensatory emphysema and hypertrophic emphysema should always be borne in mind. In hypertrophic emphysema the pulmonary capillaries are thinned out because of the overdistention of the elastically weak alveolar walls, whereas in compensatory emphysema the distention of the alveoli is a result of the overfilling of the pulmonary capillaries. When the pulmonary capillaries are compressed in one area of the lung, the blood is necessarily diverted to the other pulmonary capillaries, and if the right ventricle compensates well, it drives the same amount of blood *per same unit of time* through a lesser capillary bed, which naturally occasions an overfilling in each pulmonary capillary. This overfilling of the capillaries which surround each alveolus brings about an overdistention of the functioning alveoli.

Yates,[4] in discussing the existence of an air cell-capillary gear, points out that the air cells and capillaries are not only intimately associated functionally but also closely related physically, and if tortuous capillaries are straightened and elongated by increased unit volumes of blood, the walls of corresponding air cells are carried with them and inflation results. This has been proved experimentally by surrounding a distensible elastic bag with empty rubber tubes and filling these tubes with fluid, which will cause a distention of the elastic bag. By ligating one pulmonary artery in an animal a marked compensatory emphysema in the contralateral lung results. The same has been observed clinically in cases treated with artificial pneumothorax.

The development of compensatory emphysema will take place also in the functioning portion of the treated lung, provided the intrapleural pressure does not exceed the pulmonary intravascular tension, and the more slowly the collapse is produced the easier it is for the right heart to compensate, keeping the pulmonary circulation more competent, which insures a better oxygenation and ventilation of the lung, as can be studied by frequent spirometry.

CHANGES IN VITAL CAPACITY

The vital capacity modifications during the course of artificial pneumothorax treatment are very characteristic, and careful periodic spirometry affords a great deal of information about the respiratory

3. Bendove, R. A.: The Circulatory Changes in Artificial Pneumothorax, Am. Rev. Tuberc. **12**:107 (Oct.) 1925.

4. Yates, J. L.: The Significance of Vital Capacity in Intrathoracic Therapy, Arch. Surg. **10**:477 (Jan.) 1925.

recuperation of the lungs and how to regulate the insufflatory amounts. In an article on this subject [5] I discussed lengthily the mechanism and the factors modifying the vital capacity and indicated the clinical and prognostic value in the collapse therapy. Suffice it to mention here that the vital capacity in cases treated with expansile pneumothorax is not reduced much throughout the treatment. There is never a quantitative relation between the amount of air introduced into the pleural cavity and the reduction of the vital capacity. For instance, if the vital capacity is 2,500 cc. before inflation, it will be about 2,300 after the injection of 500 cc. of air into the pleural cavity, i. e., a reduction of only 200 cc. in the vital capacity, though 500 cc. was given. This is explained by the fact that the *residual air* of the functioning portion of the treated lung is expelled with each deep expiration, becoming an integral part of the vital capacity. The participation of the residual air in the vital capacity explains why patients treated with artificial pneumothorax of the expansile type are less dyspneic than other tuberculous patients with the same low vital capacity.

In cases in which the low vital capacity is due not to anatomic extent of the lesion but to severe toxemia caused by this lesion, it might even increase after the establishment of pneumothorax of the expansile type, as it was demonstrated in the following case:

The patient was very dyspneic on admission, had high fever and marked general malaise. The vital capacity was 1,600 cc. Physical and roentgenologic examinations revealed an extensive basal lesion of the exudative type in the right lung. After initiation of pneumothorax therapy the condition remarkably improved. The pneumothorax was of the expansile type. Three months after initiation of pneumothorax therapy, the patient had been practically symptomless and her vital capacity was 2,100, an increase of 500 cc. Frequent roentgenologic observations showed the diseased portion completely compressed, while the upper lobes continued to expand and contract with each respiratory phase. There is no doubt that the low vital capacity prior to the pneumothorax was due to the severe toxemia, but after the abatement of all the toxic symptoms during this therapy, the vital capacity returned to its physiologic point. However, if large amounts of air were introduced compressing also its functioning portion of the treated lung, the vital capacity would have remained greatly reduced.

It is obvious enough that the greater the extent of the expansile portion of the treated lung, the less the vital capacity is reduced, and vice versa.

CLINICAL CONSIDERATIONS

Because of the pneumodynamic principles just discussed, gas introduced into the pleural cavity can be made to localize over the diseased portion of the lung, provided no adhesions exist and the gas is given in the proper amounts. It is to be remembered that we administer gas

5. Bendove, R. A.: The Vital Capacity in Artificial Pneumothorax, Arch. Int. Med. **36**:94 (July) 1925.

not with the purpose of compressing the *entire* lung, but to keep the *diseased portion* alone at rest. It is out of the scope of this article to go into a discussion whether the benefit of pneumothorax therapy is due only to the rest of the diseased lung or also to certain immunologic reactions that might follow the collapse. This has been discussed fully in another article [6] and a theory was advanced to explain why healing at times takes place by resolution instead of fibrosis in cases treated with the expansile type of pneumothorax.

However, it is to be emphasized that it is possible to keep the diseased portion compressed without curtailing all the function of the uninvolved part of the same lung. Of course, when the entire lung is affected no expansile type of pneumothorax can be expected, but when only a portion of the lung is involved the expansile type of pneumothorax is the treatment of choice.

The amount of air to be given at initial inflation should never exceed one-seventh the vital capacity of the patient; the subsequent refills should be guided not only by the vital capacity but also by the principles of gas localization outlined above. No generalization as to the amount of air to be given can therefore be made, but each case should be individualized, depending on the extent of the involved and uninvolved portions of the treated lung. These can be accurately studied only by frequent roentgenoscopic examinations.

Furthermore, the insufflatory amounts and the intervals at which they are to be given differ often even in the same person. Frequent physical examinations, roentgenoscopic observations, spirometry and careful study of the circulatory changes are the best criteria how to modify the refills. The amounts may vary from 200 to 400 cc., and the intervals from five to ten days the first few months. It is to be remembered always that the gas is given with the purpose of keeping the diseased portion alone compressed, and only by frequent refills in small amounts can the gas localization be brought about.

The patients successfully treated with the expansile type of pneumothorax are usually young persons with a soft or exudative type of lesion of not very long duration, the pleura of which is free from adhesions. Such patients usually have a good cardiac reserve and the elasticity of their lungs is at its best, leading to a development of compensatory emphysema which assists in better ventilation of the lung, preventing undue dyspnea.

Complications, particularly pleural effusions, seem to be much less frequent in cases treated with this type of artificial pneumothorax. However, no definite statement can as yet be made in this respect. Further observations are necessary.

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6. Bendove, R. A.: Resolution and Healing in Pulmonary Tuberculosis, M. J. & Record **121**:36 (Jan. 7) 1925.

THORACOPLASTY VERSUS ARTIFICIAL PNEUMOTHORAX OF THE EXPANSILE TYPE

It is not the purpose of this article to go into details of the comparative advantages and disadvantages of artificial pneumothorax and thoracoplasy. Alexander [7] has gone into this question carefully in his book on thoracic surgery in pulmonary tuberculosis, to which the reader is referred. However, Alexander failed to consider the fact that artificial pneumothorax per se is not as yet a standardized method, but may in itself be divided into several types, each of which has a different action on the treated lung. In my article on the classification of artificial pneumothorax and the clinical value of the several types [1] I stated that "statistics on the result of artificial pneumothorax, so far collected, have little value because the kind of pneumothorax used in each case was never taken into consideration, and thus altogether unequal elements were being compared, inasmuch as the various pneumothoraces act on normal and pathological lung tissue in mechanically and physiologically different ways."

Furthermore, in evaluating the mode of action and results of treatment of either pneumothorax or thoracoplasty, we must take into consideration the type of pulmonary tuberculosis on which these methods were used. The difference between the productive or proliferative types and the soft caseous or exudative types of tuberculosis should always be kept in mind. The soft caseous lesion or the exudative types represent a condition in which the body shows little reaction in the way of defense and the process of destruction preponderates over the process of repair in the pulmonary tissue, whereas the proliferative or productive type indicates a preponderance of granulation tissue which is being produced at the site of the lesion. This division is not only an anatomic-pathologic differentiation, but it denotes a definite clinical differentiation; the proliferative variety usually is chronic in type and may exist for many years without any clinical manifestation, whereas the exudative variety usually is of the acute or subacute type giving rise to symptoms early in its development.

It is in the proliferative type of pulmonary tuberculosis that thoracoplasty is to be resorted to, as when such patients begin to show symptoms the lesion is usually far advanced with marked pleuritic adhesions, rendering pneumothorax unavailable. The exudative type of pulmonary tuberculosis, on the other hand, will benefit little by thoracoplasty, because the latter never compresses the diseased part fully and the stimulation to fibrous tissue formation is not very successful in such cases. As was indicated above, such types of pulmonary tuber-

7. Alexander, J.: Surgery of Pulmonary Tuberculosis, Philadelphia, Lea & Febiger, 1925.

culosis usually manifest themselves clinically early in their evolution, in their first or second stage of anatomic involvement, and the treatment of choice is the expansile type of pneumothorax, which effects a complete compression of the diseased portion without reducing very much the function of the nondiseased portion of the treated lung.

A comparison of figures 1 and 17, two roentgenograms of the same patient, one taken prior to initiation of pneumothorax and the other taken five months later, shows the remarkable result obtained by the expansile type of pneumothorax. The cavity has become obliterated and the entire lesion has been compressed and reduced to its minimum. The same results were obtained in the basal lesions, as seen from comparison of figures 5 and 8. This could never have been accomplished by thoracoplasty, even if the entire length of the ribs was removed. Furthermore, the nondiseased portion of the treated lung was affected only slightly, its ventilatory function becoming at times even more efficient, as was discussed fully in considering the circulatory changes and the vital capacity.

Thoracoplasty has been considered as the ultimum refugium treatment in pulmonary tuberculosis; still the modern thoracic surgeon hopes—and perhaps rightly so—"that the specialists in tuberculosis will soon refer for surgery many patients whose disease is far less advanced than are those who are at present being operated upon," [7] and any one will endorse the following statement of Graham [8] in regard to thoracic surgery:

> In the future it will unquestionably be made safer by better understanding of the physiology and pathology involved, by a more precise drawing of operative indication, and by a closer cooperation between the internists and surgeons, which will permit the carrying out of operative procedures at a time when they may prove of real benefit with a minimum risk instead of being last resorts in patients who are already nearly dead.

Artificial pneumothorax, rightly belonging to the domain of thoracic surgery, though because of the long period of time its application requires it is considered as a "medical" treatment, is still looked on by many as a last resort measure in the treatment of pulmonary tuberculosis. In view of this newer understanding of the mechanism and effect on the diseased and nondiseased lung tissue, pneumothorax, particularly of the expansile type, should be recognized as the treatment of choice in the exudative type of pulmonary tuberculosis, and is to be administered as early as possible. It throws little burden on the respiratory function of the contralateral lung; it effects complete compression of the diseased portion without curtailing the function of the nondiseased portion of the treated lung; it makes little demand on the

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8. Graham, E. A.: Recent Phases of Thoracic Surgery, J. A. M. A. **80**:1825 (June 23) 1923.

cardiac reserve; it reduces the vital capacity but little, if any, and the gradual development of compensatory emphysema in the functioning portion of the treated lung replaces and fills the hemothorax gradually without causing any deformity. A slight or even moderate involvement of the contralateral lung is not a contraindication for this therapy, because in this type of pneumothorax little extra demand, if any, is made on the respiratory function of the other lung.

CONCLUSIONS

The difference in the elasticity of the diseased and nondiseased lung tissue as well as the difference in the intrapulmonary and intrapleural pressures make it possible for the introduced gas into the pleural cavity to localize itself over the diseased portion without curtailing much of the function of the unaffected portion of the treated lung, provided the amounts administered are small and are given at frequent intervals. These pneumodynamic principles should be made use of in every case treated with artificial pneumothorax; they are best applied, however, in cases of the exudative type of pulmonary tuberculosis of not very long duration which are free from pleural adhesions. In such cases pneumothorax therapy is not to be considered as a last resort measure, but as the treatment of choice, as it offers a more speedy and more complete anatomic and functional recovery.

These pneumodynamic principles of gas localization cannot, as a rule, be applied in cases of the productive or proliferative type of pulmonary tuberculosis, because such cases usually run a mild clinical course, and when they begin to manifest severe symptoms they are usually far advanced and marked pleuritic adhesions are present, rendering a therapeutic pneumothorax inapplicable. In such cases thoracoplasty is the indicated treatment provided the contralateral lung is in good condition.

A slight or even a moderate involvement of the other lung is not a contraindication for artificial pneumothorax of the expansile type, because the function of the undiseased portion of the treated lung is not curtailed much, and little demand is made for extra respiratory function on the other lung. The insufflatory amounts in such cases should vary from 200 to 400 cc. of air and the intervals from five to ten days. No generalization can be made, but each case is to be individualized, depending on its vital capacity and extent of involved and uninvolved portions of the treated lung. This can be studied only by frequent roentgenoscopic observations and periodic spirometry.

INVOLUTIONAL OR REGRESSIVE CHANGES IN THE THYROID GLAND IN CASES OF EXOPHTHALMIC GOITER

AND THEIR RELATION TO THE ORIGIN OF CERTAIN OF THE SO-CALLED ADENOMAS *

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BALTIMORE

INTRODUCTION

Nearly a century has now passed since Robert Graves [1] in 1835 first described the clinical syndrome that at present bears his name and characterized this disease as being due to an hypertrophy of the thyroid gland. The first descriptions of the histologic changes occurring in hypertrophy and hyperplasia of the thyroid gland were made in 1886 by Horsley [2] and in 1896 by Halsted,[3] when they reported the compensatory changes occurring after partial thyroidectomy in animals. Greenfield [4] in 1893 expressed the belief that certain specific changes occurred in the structure of the thyroid gland in exophthalmic goiter and this has been confirmed by many observers, most notable among whom are Lewis,[5] MacCallum,[6] Hanseman,[7] Lubarsch,[8] Ewing,[9] Wilson,[10] MacCarty [11] and Kocher.[12]

The studies made by these observers have been so detailed and complete that little new has been added to this subject in recent years, and the histologic changes occurring when the thyroid gland undergoes hypertrophy and hyperplasia, whatever the degree, are today fairly well

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* From the Department of Surgery of Johns Hopkins University.

1. Graves, Robert: Clinical Lectures, 1835, Philadelphia, Adam Waldie, 1838.
2. Horsley, Victor: Brown Lectures, Lancet **2**:1163 (Dec. 19) 1886.
3. Halsted, W. S.: An Experimental Study of the Thyroid Gland in Dogs with Special Consideration of Hypertrophy of the Gland, Johns Hopkins Hosp. Rep., 1896, p. 373.
4. Greenfield, W. S.: Some Diseases of the Thyroid Gland, Brit. M. J., 1893.
5. Lewis, Dean: The Pathological Anatomy of Exophthalmic Goiter, Surg. Gynec. Obst. **3**:476, 1906.
6. MacCallum, W. G.: Pathology of Exophthalmic Goiter, J. A. M. A. **49**:1158-1162 (Oct. 5) 1907.
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11. MacCarty, W. C.: Mayo Clinic Papers, **13**, 1912.
12. Kocher, Albert: Arch. f. path. Anat. **208**:86; 161, 1912.

understood. It is now a well recognized fact that there exists, clinically, different degrees of hyperthyroidism, from the most mild to the most severe; the latter syndrome usually comes under the classification of exophthalmic goiter. The clinical course of the cases of exophthalmic goiter also varies to a great extent; for instance, the most severe or fulminating cases have, as a rule, a relatively acute onset followed by a short, unremitting course of the disease which, if allowed

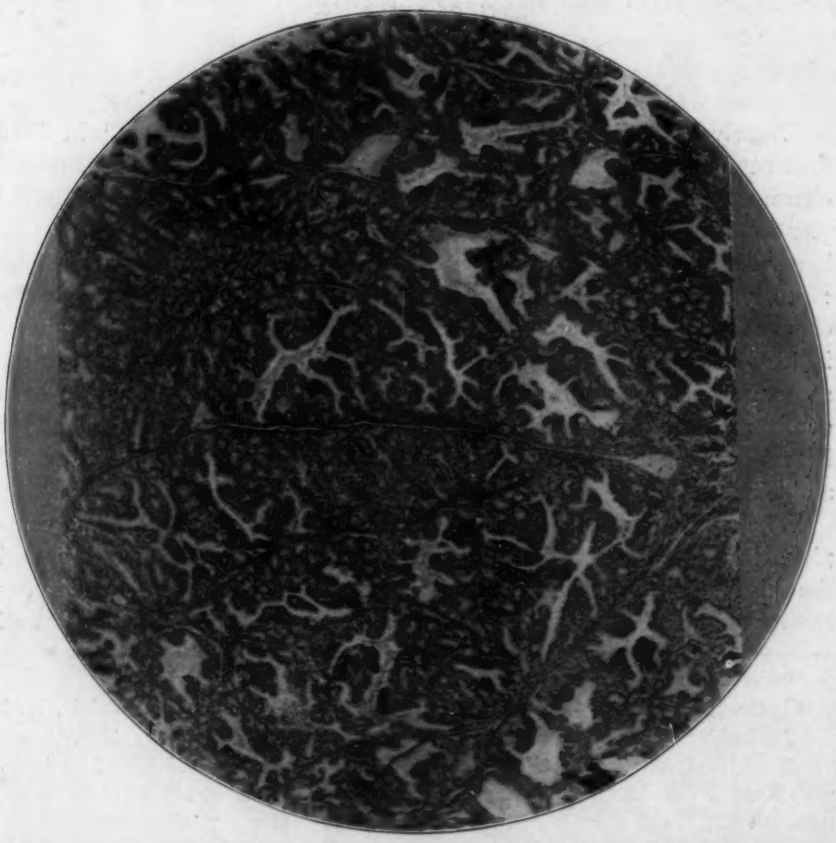

Fig. 1 (case 1).—One of a series of sections of excised right lobe before involution or administration of iodine, under low power (40 mm. lens); classical histologic structure of extreme hypertrophy and hyperplasia seen in a typical case of exophthalmic goiter; marked increase in parenchyma and decrease in colloid spaces; fibrous tissue increase plain in lobulation of gland; some lobules made up entirely of small acini.

to progress untreated, ends in death in a large percentage of the cases. In the less severe cases the clinical course consumes a great deal more time and is attended with one or more remissions and exacerbations even though it remains untreated throughout its course.

In the more mild cases of hyperthyroidism not severe enough to be classified as exophthalmic goiter the occurrence of remissions and exacerbations is of still greater frequency. In all instances of hypertrophy and hyperplasia of the thyroid gland whether pathologic or physiologic, remissions and exacerbations occur, with the exception of the acute fulminating cases of exophthalmic goiter mentioned above, in which remissions do not occur. In general there is a definite parallelism

Fig. 2 (case 1).—Figure 1 under higher magnification (× 176); dilated vessels, lymph and blood in stroma, very active hypertrophy and hyperplasia of epithelium readily seen; acini empty except for clear, nonstaining vacuoles; mottling of epithelium and vesicular character of nuclei are evident; epithelium thrown up in folds like papillomas; colloid not abutting on epithelium.

between the severity of the clinical course and the histologic changes observed, although in some clinically typical cases the microscopic picture of the thyroid gland is a source of great surprise and subject to the most extensive variations. The result is that many different classifications

have been made for the various microscopic alterations observed but these, up to the present time, have been without a great deal of significance.

In the past a detailed study has been made of the changes in the histologic structure of the thyroid gland resulting from all degrees of hypertrophy and hyperplasia, from the most simple type observed in

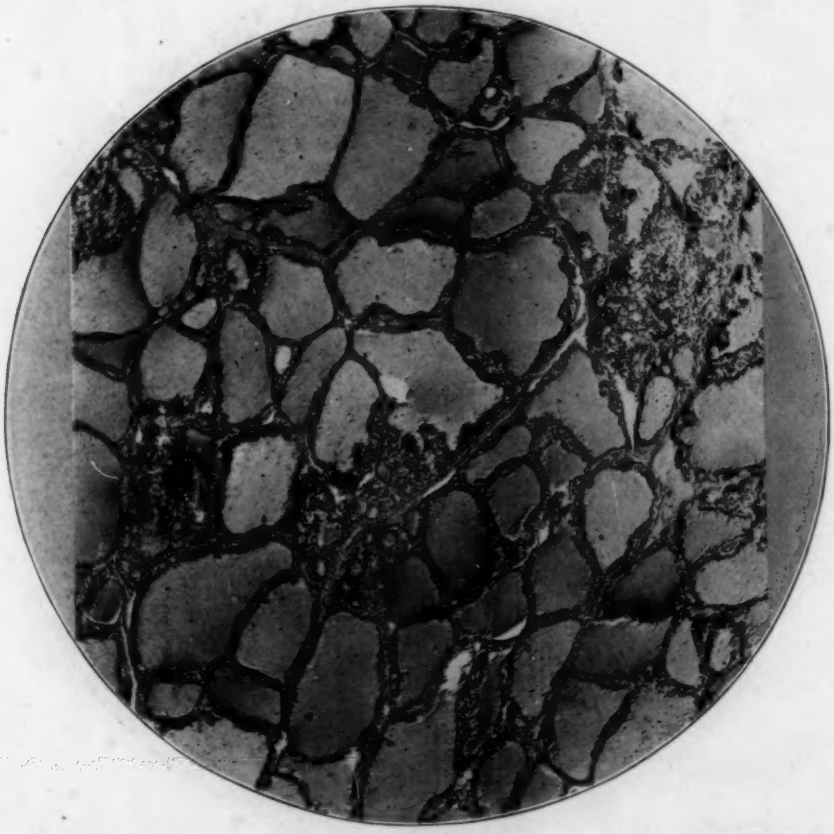

Fig. 3 (case 1).—Typical section of series made of entire gland of case 1 (40 mm. lens) after administration of iodine for three weeks; striking contrast to figure 1 is seen although from same patient; colloid spaces are in great predominance over strikingly decreased amount of parenchyma; this represents the average degree of involution occurring in the gland of this patient.

puberty and compensatory hypertrophy to that occurring in the most extreme hypertrophy and hyperplasia of exophthalmic goiter. However, the changes in the histologic structure of the thyroid gland during a clinical remission or resulting from involution of the gland have not

been considered at all in the human being, and only slightly in animals.[13] The reasons for this are quite obvious, for until recent years there has been no method at hand which enabled an examiner to decide whether a patient was beginning an exacerbation or a remission. The personal equation entering into the clinical interpretation varied far too much for any dependence to be put in this method of classification. It is now

Fig. 4 (case 1).—Figure 3 after administration of iodine, under higher magnification (176 mm. lens); acini more regular in shape although some mounds of infolding epithelium still persist; acini flattened out from increased amount of colloid; epithelium in figure 4 as compared with figure 2 shows marked flattening in figure 4; acini completely filled with evenly stained colloid throughout, which abuts on epithelium; small areas of persistent hyperplasia seen in figures 3 and 4; nuclei pyknotic.

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13. De Ligneris, quoted by Kocher, T.: Brit. M. J. **1,** 1906. Marine, D., and Williams, W. W.: The Relation of Iodine to the Structure of the Thyroid Gland, Arch. Int. Med. **1**:349-384 (May) 1908. Helwig, Alexander: Zur Post operativen Kropf prophylaxe (Histologie der Hunde-Rattenschilddrüse noch Iod Futterung), Arch. f. klin. Chir. Kongressband **126.**

recognized that the determination of the basal metabolic rate over a period of time of sufficient length affords an excellent index of the activity of the thyroid gland so that at present a method is available which makes possible the approximate standardization and registration of the degree and amount of hyperactivity or hypo-activity of the thyroid gland. This not only eliminates the error of personal equation of the examining clinician but also on the part of the patient. Again, a spon-

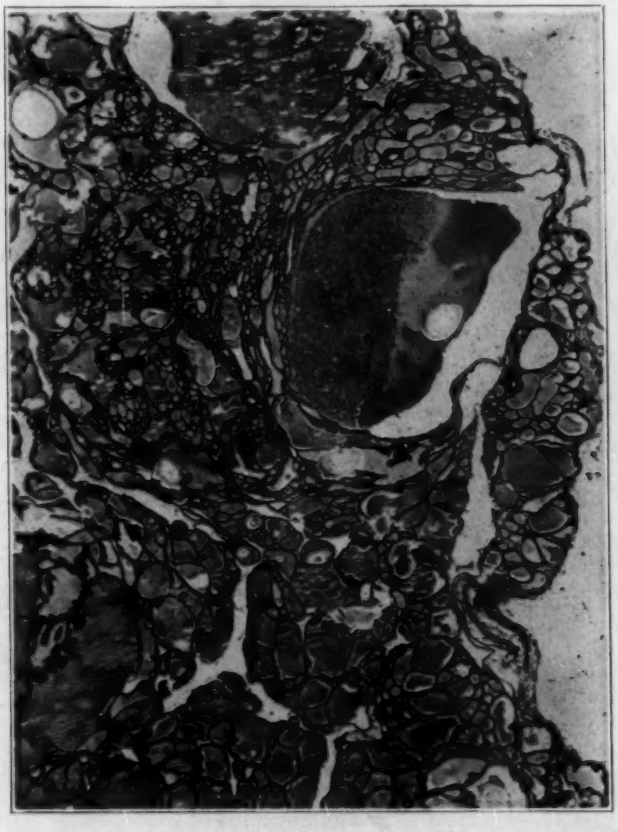

Fig. 5 (case 1).—Large section of gland of patient 1 showing areas of hyperinvolution, under very low power (×16); these areas are confined to a lobule compressing the parenchyma in the periphery of the lobule; the areas resemble colloid cysts and colloid adenomas; none of these areas were present in any sections of the gland previous to the involution as a result of the administration of iodine; the involution of the gland about these areas was of average degree for the gland as a whole.

taneous remission as a rule occupies a long period of time and when completed approximates to a greater or less degree the physiologic status of a normal individual and the histologic structure of a normal thyroid gland. So that an examination of the histologic structure of

the thyroid gland at any one point during a remission does not offer an opportunity to study the microscopic changes that have occurred in that gland concomitant with the clinical remission. This is due, of course, to a lack of knowledge of the microscopic appearance of the thyroid gland before the onset of the remission. Mainly for these reasons, it has been impossible in the past to note the microscopic alterations in the thyroid gland due to the changes of involution. With the reintroduction of

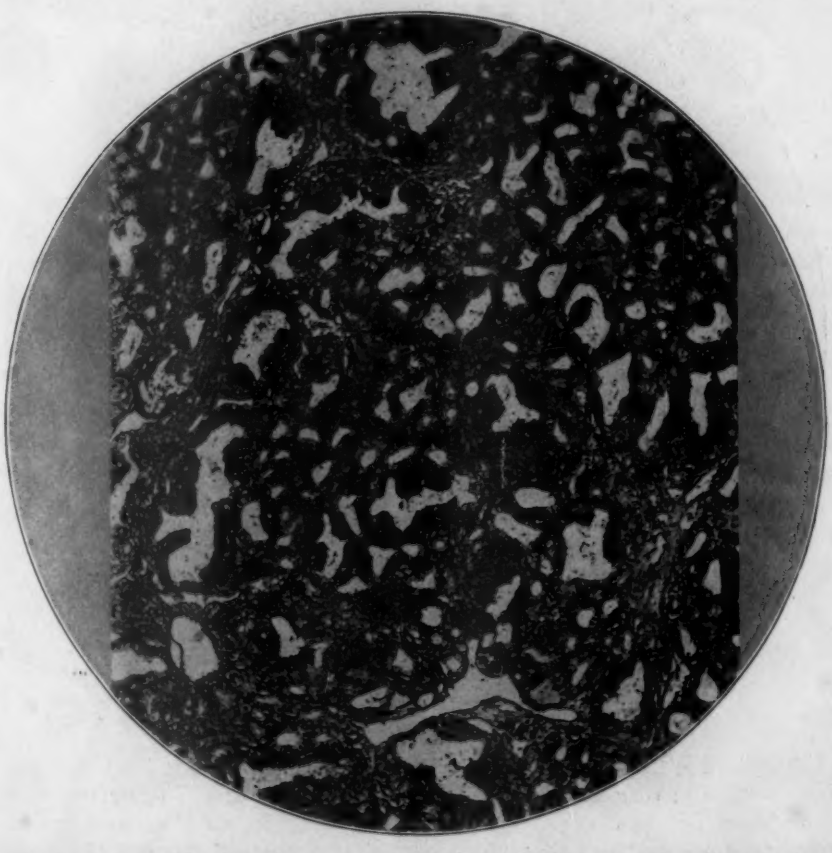

Fig. 6 (case 2).—Gland before involution or administration of iodine (× 40); typical section of series of upper portion of right lobe including right upper pole; typical exophthalmic hypertrophy and hyperplasia.

iodine in the treatment of exophthalmic goiter a method of producing a precipitous clinical remission was obtained. The most acute and fulminating cases of exophthalmic goiter could be transformed in a period of from two to six weeks into a clinical condition which, in many cases, approximated normal or, at least, a state of a very low grade of hyperthyroidism. This observation has been made many times and

reported.[14] By means of standard doses of iodine, together with the control of the period of time over which it was given, with frequent determinations of the basal metabolic rate, one was enabled to divide the clinical remissions into different periods of completion.

Fig. 7 (case 2).—Section after involution had occurred from iodine administration (× 40); comparison should be made with figure 6; this figure represents the average degree of involution for this case, seen in the gland as a whole; some asymmetry of the acini; interacinous stroma quite delicate and epithelium much flattened so that nuclei stand out on stroma; evenly stained colloid completely filling acini; no vacuoles.

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14. Plummer, H. S., and Boothby, W. M.: The Value of Iodine in Exophthalmic Goiter, J. Iowa S. M. Soc. **14**:66 (Feb.) 1924. Starr, P.; Wolcott, H. P., and Means, J. H.: The Effect of Iodine in Exophthalmic Goiter, Arch. Int. Med. **34**:355-364 (Sept.) 1924. Thomas, H. M., and Rienhoff, W. F., Jr.: Iodine in the Treatment of Hyperthyroidism, South. M. J. **19**:87 (Feb.) 1926. Rienhoff, W. F., Jr.: Histological Changes Brought About in Cases of Exophthalmic Goiter by Administration of Iodine, Bull. Johns Hopkins Hosp. **37**:285 (Nov.) 1925.

METHOD

To determine the changes occurring in the histologic structure of the thyroid gland which accompanied a clinical remission an examination of the miscroscopic structure of the thyroid gland before the onset of the remission was made. This was accomplished by selecting a series of seven cases of acute fulminating exophthalmic goiter of short duration in which no spontaneous remission had occurred and also in which no form of iodine or treatment of any type had been administered. These

Fig. 8 (case 2).—Section across entire lobe of patient 2 under very low power (× 16) after involution to show asymmetrically placed hyperinvoluted areas that occurred in gland during involution; these resemble colloid adenomas, histologically, the remainder of the gland around these areas undergoing the average amount of involution; no such areas were present in large portion of gland removed before iodine administration.

cases were also selected from a larger group because, following the administration of iodine in each, there was established a typical artificial clinical remission to a condition closely approximating normal. In each of these cases careful clinical and laboratory examinations on admission, including two basal metabolic rate estimations, revealed the fact that

they all presented a clinical picture of a typical case of extreme exophthalmic goiter with their basal metabolic rates varying from 60 to 80 per cent above normal. It is not thought necessary to describe the clinical signs and symptoms of this series except to state that the thyroid gland in each seemed to be increased two or three times in size above normal, was soft and vascular, thrills and bruits occurring at all four poles.

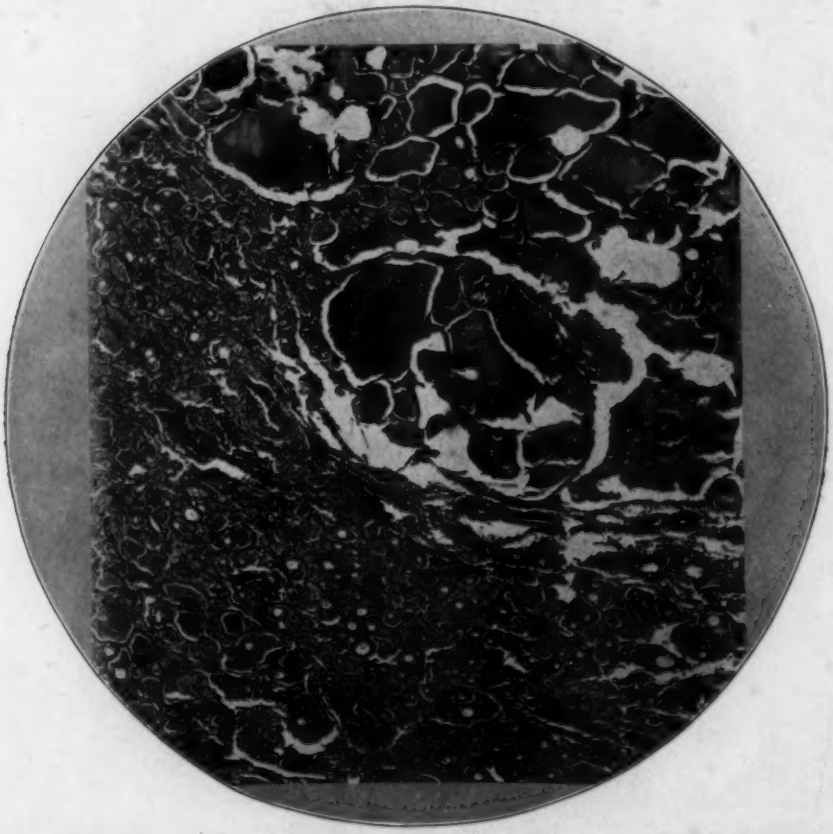

Fig. 9 (case 2).—Figure 8 under higher power (×40) showing histologic details of hyperinvoluted areas; compression of tissue at periphery; localized and encapsulated dilated colloid acini; same microscopic picture observed in many areas of the gland after involution; the gland in the adjacent regions is undergoing the average amount of involution.

The glands were diffusely enlarged throughout and in them no nodules of any size could be palpated.[15] Under local anesthesia a large portion of the entire right lobe including all of the right upper pole of the thyroid

15. A preliminary report of this study was published in Bull. Johns Hopkins Hosp. **37**:285 (Nov.) 1925.

gland was excised before treatment was instituted. This portion of the gland was then fixed immediately at the operating table in different fixatives, namely, Zenker's solution with 10 per cent formaldehyde, Zenker's solution, Bensley's acetic-osmic bichromate solution containing osmic acid solution, 2 per cent, glacial acetic acid, 1 grain, and potassium bichromate solution, 2.5 per cent. Large and representative serial

Fig. 10 (case 3).—Typical picture of exophthalmic hypertrophy (×40); lymphocytic infiltration, absence of colloid, and characteristic section of large portion of right lobe excised before administration of iodine should be noted.

sections were obtained from this excised portion by cutting them transversely across the entire block of tissue. The sections varied in thickness from five to ten microns. The circulation through the remainder of the thyroid gland was disturbed as little as possible. In this manner a careful and detailed study was made of the microscopic appearance and the histologic structure of the thyroid gland in an acute case of exophthalmic goiter at the height of the disease and before any treatment was administered. These patients were then given a com-

pound solution of iodine (10 minims) four times a day, for periods varying from two to four weeks and observed continuously during the administration of the iodine. The estimation of the basal metabolic rates were recorded frequently, every five days. In all cases a definite clinical remission was established, the patient improving remarkably, and the basal metabolic rates fell well below 20 per cent above normal.

Fig 11 (case 3).—Typical amount of involution occurring in gland as a whole after administration of iodine (× 40); slightly more than usual vacuolization; some infolding of epithelium; according to Aschoff's and Kocher's terminology, this would be called either struma diffusa colloides macro follicularis proliferans or struma colloides Basedowiana; some acini are larger than others and distention of these has thinned the walls. Comparison should be made with figures 10 and 11.

Operation was then performed on these patients, at which time a double partial lobectomy of the thyroid gland was done. These specimens were immediately fixed as above noted and again serial sections were cut from all portions of the gland removed. Thus, an opportunity was afforded

to compare the histologic changes in the thyroid gland observed at the height of the disease with the microscopic alterations occurring in the gland concomitant with a clinical remission. As the histologic structure of the several glands of this series showed the same alterations and changes before and after the remission and involution, they will be described collectively as a group of cases rather than individually, thus obviating needless repetition. In order to demonstrate the full extent

Fig. 12 (case 3).—Gland after involution of iodine (× 80); area of hyper-involution that is beginning to be demarcated from the rest of the gland by involuting more completely than the average amount throughout the gland; comparison should be made with figure 10; vacuolization of the colloid at one point opposite one side of the middle acinus where there is proliferation of the epithelium on the one side only seems to bear out Aschoff's idea of there being a germinal center in each follicle which is the center from which new acini develop; however, in the light of figure 10 we know that this stage is less active, histologically and clinically, and instead of being, as one would suppose if only this section were obtained without a previous standard for comparison, a point of beginning proliferation it is one of the last dying embers of proliferation.

of the histologic transformations during the involution, and also to show the microscopic appearance of the type of thyroid gland existing in this series before the involution occurred, a full description of the hypertrophy and the hyperplasia occurring in the thyroid glands of these cases is given.

GROSS AND MICROSCOPIC APPEARANCE OF THE THYROID GLAND AT THE HEIGHT OF THE DISEASE BEFORE THE INVOLUTION ESTABLISHED BY THE ADMINISTRATION OF IODINE

Gross Appearance.—The tissue was soft and elastic, very vacular and had the typical raw beef appearance so often observed in exophthalmic goiter. On palpation it imparted a characteristic gland like feel, entirely devoid of any areas of increased or decreased density. The cut surface was coarsely and finely lobulated and somewhat granular in appearance. As a whole, the tissue was of uniform opacity and little or no colloid could be observed.

Microscopic Appearance.—Everywhere the gland was divided into lobules by a fibrous tissue stroma that was definitely increased above normal although relatively delicate. This stroma divided the lobes into lobules which in turn were redivided by the intralobular septums, the latter surrounding completely the follicles or acini. Occasionally large bands of scar tissue traversed the gland, regardless of its lobulation. Throughout the interlobular and intralobular stroma many dilated blood and lymphatic vessels occurred which were distinguished mainly by the contents of the former. The most striking characteristic of the microscopic picture of exophthalmic goiter is well shown in figures 1, 2, 6 and 10; namely, the marked predominance of the parenchyma and the equally pronounced diminution of the colloid. There seem to be two types of hypertrophy and hyperplasia of the thyroid gland which, in this series of cases, were about evenly distributed throughout the gland; that is, in some areas one encountered lobules made up purely of small round acini containing practically no colloid, or if any, at the most a mere drop. The small acini were closely packed together, being held by a very delicate stroma through which coursed many dilated blood vessels. The more developed of these smaller acini seemed to occur toward the center of the lobule, the younger ones being arranged in the periphery (fig. 1). The epithelial cells in these small acini were so closely arranged that their apexes abutted on each other (fig. 19). The other types of hypertrophy and hyperplasia referred to were the larger lacelike papillomatous acini which were very irregular in shape and uniformly larger in size (figs. 1, 6 and 10). In some lobules the two types of hypertrophy were present together and in this event the larger lacelike acini, as a rule,

were in a more central situation with the smaller acini toward the periphery. The colloid was very scant and in many acini totally absent; when present it stained very poorly, being shreddy, granular, vacuolated and watery-like in appearance (figs. 1, 6 and 10). The vacuoles, as a rule, were interposed between the central portion of the colloid and the edges of the epithelium. The papillomatous infolding of the epithelium, in the majority of these larger acini, almost completely filled the lumen

Fig. 13 (case 3).—Area of hyperinvolution in large colloid cyst developing during involution (×40); flattened epithelium lining cyst which contains densely stained colloid without any vacuoles; compression of tissue about cyst evident; development of capsule from intralobular and interlobular stroma is shown, also flattening of small peripheral acini.

so that the spaces available for the collection of colloid appeared as mere slits in the lobules (fig. 1). Occasionally acini were found which contained large numbers of desquamated epithelial cells and red blood cells (figs. 1, 6 and 10).

The epithelium differed slightly in the large and small acini but on the whole showed the same fundamental changes. In the larger acini the epithelial cells were tall, columnar cells and very active in appearance (fig. 2). These cells stained lightly and contained large vesicular nuclei which were situated at the base of the cells. The contour of the cell, besides being columnar, was somewhat barrel shaped, being convex at the apex and along the sides, the cells seeming to bulge with their

Fig. 14 (case 4).—Areas of hyperinvolution that had resulted in the formation of two large colloid cysts (× 16); this is a very low power photograph; these areas developed during involution. The histologic appearance and microscopic structure of the thyroid gland of patients 4 and 5 before involution were similar in all respects to those of patients 1, 2 and 3; therefore it was not felt necessary to print them.

contents or presecretion bodies. The cytoplasm contained numerous mitachondria which did not appear to have any special polarity but were diffusely scattered throughout the cell. They occurred in rods of different lengths and shape. The chromophobe vacuoles were numerous and

stood out because of the inability to stain them. They seemed to be situated in a fine, granular network of cytoplasm which took a faint pink stain. Colloid droplets were not infrequently observed; they were usually situated in the apical end of the cell or alongside the nucleus, being best seen with Bensley's mitachondrial stain or neutral gentian violet. It would seem that these colloid droplets were much more scarce in the very active gland. The nuclei contained a fine chromatin network

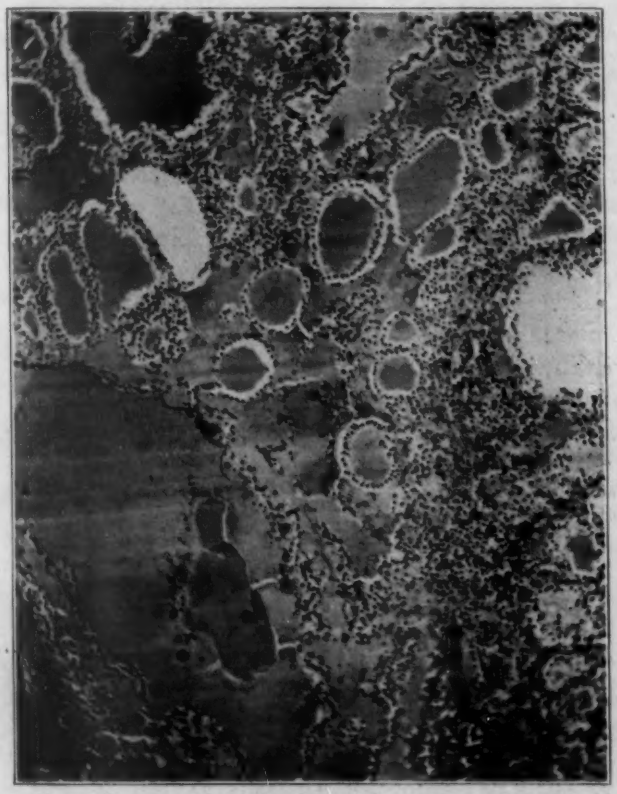

Fig. 15 (case 4).—Areas of extreme hyperinvolution termed in this study as the third type that approximates degeneration (×67); inequality in size of acini, extreme involution of epithelium and pyknotic nuclei; disintegrating acini, with the result that small clumps of epithelium are deposited in the abundant stroma; the stroma here is partly made up of colloid which has escaped from the acini due to this disintegration; this type of disintegration is frequently seen in areas of extreme involution.

with granules and from one to three nucleoli. Frequent mitotic figures were seen. In the smaller acini, the epithelial cells were not, as a rule, as high as the columnar cells of the larger acini but were more square in shape, being a rather low columnar cell. Otherwise, these cells did not

differ materially from the high columnar cells. Occasionally, a marked disparity was observed in the size of the nuclei of the small acini. In these sections, shown in figures 1, 2, 6 and 10, there are minor variations in the height of the epithelium, the size and the shape of the acini and the density and amount of the colloid, but as a rule the process of hypertrophy and hyperplasia is a diffuse, fairly uniform one.

MICROSCOPIC CHANGES IN THE THYROID GLAND CONCOMITANT WITH AN ARTIFICIAL REMISSION RESULTING FROM THE ADMINISTRATION OF IODINE: INVOLUTION OF THE THYROID GLAND IN EXOPHTHALMIC GOITER

Gross Appearance.—The thyroid gland in the gross was much changed. The surface instead of being smooth presented nodules and elevations varying from 0.5 to 3 or more centimeters in diameter. The gland seemed to be definitely less mobile in the neck in all directions, being bound down by periglandular adhesions. The normal fascial cleavage was disturbed and to a great extent abolished. The vascularity seemed definitely decreased, both arterial and venous. The gland itself was much more difficult to mobilize at operation and seemed to be more brittle and stiff, having lost to a great extent its elasticity. The capsule seemed bulging with the contained lobulated parenchyma and definitely thickened. On section the cut surface of the gland was glary in appearance, and from it a clear lymphlike fluid dripped, suggesting that there was obstruction to the flow of lymph in the gland—a backing up of the lymph, due to an interference with the free outflow. Cystlike areas that seemed to be filled with fluid and also dilated, localized areas of colloid could be noted in the gross (fig. 20). Besides these there were areas with a smaller amount of colloid which were more opaque and somewhat granular, appearing as elevated areas of parenchyma on the cut surface and giving one the impression of small adenomatous areas.

MICROSCOPIC APPEARANCE AFTER INVOLUTION HAS OCCURRED AS A RESULT OF IODINE ADMINISTRATION AND AN ARTIFICIAL REMISSION

The sections showed the most striking alterations when compared to the microscopic sections of the gland before iodine was administered (figs. 3, 4, 7, 11 and 12). The connective tissue elements were markedly increased in not only the interlobular and intralobular stroma or septums but also in the scarring throughout the gland. In some instances, this approached a true sclerosis of the gland. By far the most striking and significant change observed was the increase in amount of colloid and the definite change in its character. After iodine it was more heavily and uniformly stained, homogeneous, distending the acini to their capacity

and in some instances even beyond this capacity. There were still to be found areas of vacuolization of the colloid but in a far less marked degree than before iodine was given (fig. 11). The acini were much more regular in shape and size, being ballooned out as it were by the colloid until, to a great extent, the histologic picture of the normal gland was approximated, at least as near as it is possible for a thyroid gland to approximate normal, having once been the seat of hypertrophy and hyperplasia. The small, as well as the large, acini contained the same type of colloid. Some infolding of the epithelium was present, but this was much less marked and these occasional sprigs and mounds of epithelium remained as evidence of the involution of a previous hypertrophy and

Fig. 16. (case 5).—Section across entire portion of base of right lobe which contains two large colloid cysts that were developed during involution and could be palpated clinically before operation (× 10); however, before the administration of iodine or the completion of involution there were no such areas demonstrable either clinically or microscopically.

hyperplasia of the parenchyma. The lobulation of the gland was not quite as evident because of the distention of the acini and the stretching with the consequent thinning out which the septums must undergo. The same intralobular pattern of the lobule or division into acini was present, the smaller ones situated more peripherally and in some instances completely compressed or flattened. The blood vessels and lymphatics were much less apparent, being partially occluded and collapsed in the interlobular and intralobular septums by the pressure resulting from the marked increase in colloid. The epithelium lining the acini showed most extraordinary alterations when compared with the epithelium lining the acini in the glands before iodine was given. Figures 1 and 3, 2 and 4, 6 and 7, and

10 and 11 should be compared. After iodine and involution the epithelial cells were much decreased in size in general throughout the section, but in some places the decrease was greater than in others. There was always a marked diminution from the columnar type to a cuboidal or low columnar cell and in the areas of complete involution the epithelial cells not only were of the size of the normal thyroid cell but also approximated that of an endothelial cell, being flattened so much that the nuclei pro-

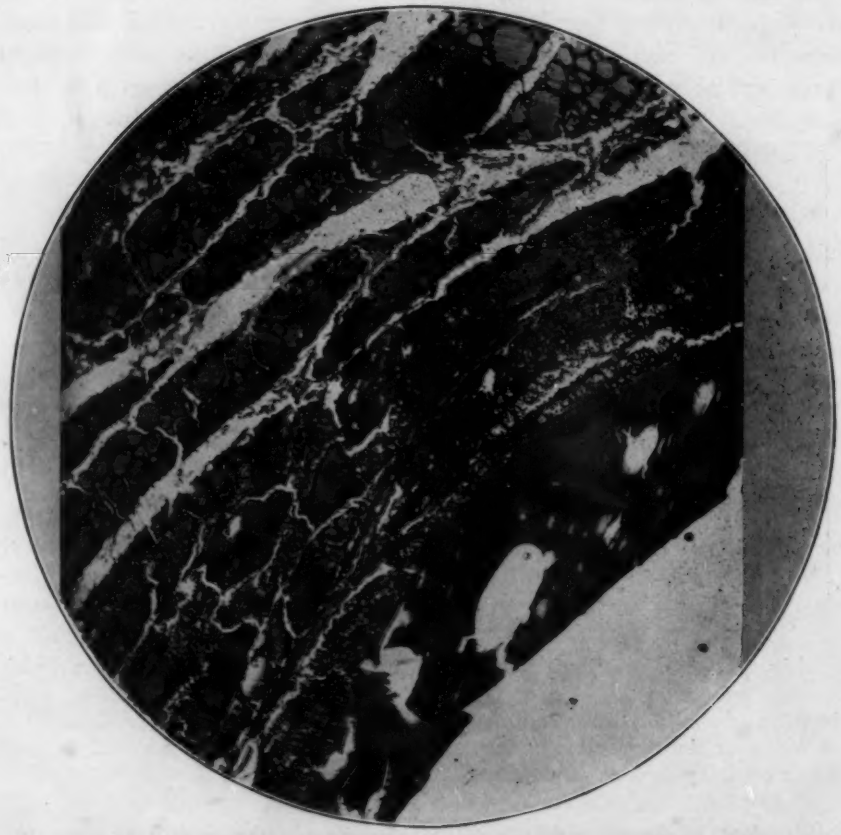

Fig. 17 (case 5).—Section taken through margin of colloid cyst shown in figure 16 (× 16); average amount of involution of gland as a whole can be seen in tissue adjacent to the colloid cyst; compression of parenchyma and flattening of peripherally placed acini due to pressure of cyst against the intralobular and interlobular stroma, which is progressing to the formation of a capsule; cyst lined with flattened epithelium.

truded beyond the cytoplasm like the pearls in a pearl necklace. The cytoplasm was much diminished in amount and the nucleus made up the main portion of the cell, so that one may say that as far as the epithelium was concerned the thyroid gland, during involution generally or diffusely,

undergoes more complete involution at certain points than at others. The tendency in general was toward complete involution and the epithelium approximated very closely the type of epithelium one sees in the simple colloid goiter. The shape of the cells also differed from that of the gland of an uninvoluted exophthalmic goiter, in that they were shrunken in appearance, the lateral walls and apexes being concave instead of convex. They seemed to have rid themselves of their intracellular contents and gave the appearance of a resting or inactive cell. The ends of the cells abutted on the colloid in the majority of acini; occasionally, however, a small number of clear vacuoles were interposed between the colloid and the apexes of the epithelial cells. The cytoplasm stained a more even pink and had lost entirely the mottled appearance seen in the exophthalmic goiters before iodine was given. No chromophobe vacuoles were observed and the cytoplasm seemed to contain many finely divided granules which were distributed evenly and diffusely throughout the cell. The mitachondria were much reduced in number and instead of appearing as rodlike structures were broken up into small granules which were also distributed diffusely throughout the cytoplasm with no especial polarity. Little difference could be ascertained in the number and size of the colloid droplets. With Bensley's method of staining for mitachondria these colloid droplets took on a rather green stain, and seemed to be situated in the apical end of the cell, near the nucleus, as a rule. The nuclei were very pyknotic and shrunken. The nucleoli were difficult to see and the chromatin granules seemed to be more numerous, causing the nuclei to be much more densely stained or basophilic. No mitotic figures were seen. The areas of lymphocytosis were much less frequent during and after involution and the areas that were present seemed to be markedly reduced in size. The general appearance of a section of the thyroid gland after iodine had been given, and a complete involution brought about, seemed to be that of a resting or inactive state of the epithelium which appeared in marked contrast to the previous condition of extreme cellular activity in the same gland before the involutional changes had occurred.

The foregoing description applies to the involutionary changes that occurred in each of the seven cases of this series of exophthalmic goiter during an artificial remission that occupied a period of time from ten to thirty days, and represents the average degree of involution that was observed to occur throughout the gland as a whole. For the sake of clearness, the degree of involution above described will be referred to as the normal and average amount occurring in the cases of this series, and the variations now to be described will be classified according to their relation to this average normal whether greater than normal or hyperinvoluted, or less than normal or hypo-involuted.

HYPERINVOLUTION

The areas of hyperinvolution observed to develop in this series of seven controlled cases could be divided roughly into three distinct types. The first type was the large colloid cyst (figs. 5, 13, 14, 16 and 20). These varied in size and number and could be found diffusely scattered throughout the gland. They usually occupied one lobule and were lined with a single layer of cuboidal epithelium, which closely approximated a normal thyroid cell in size, shape and staining capacity. There were

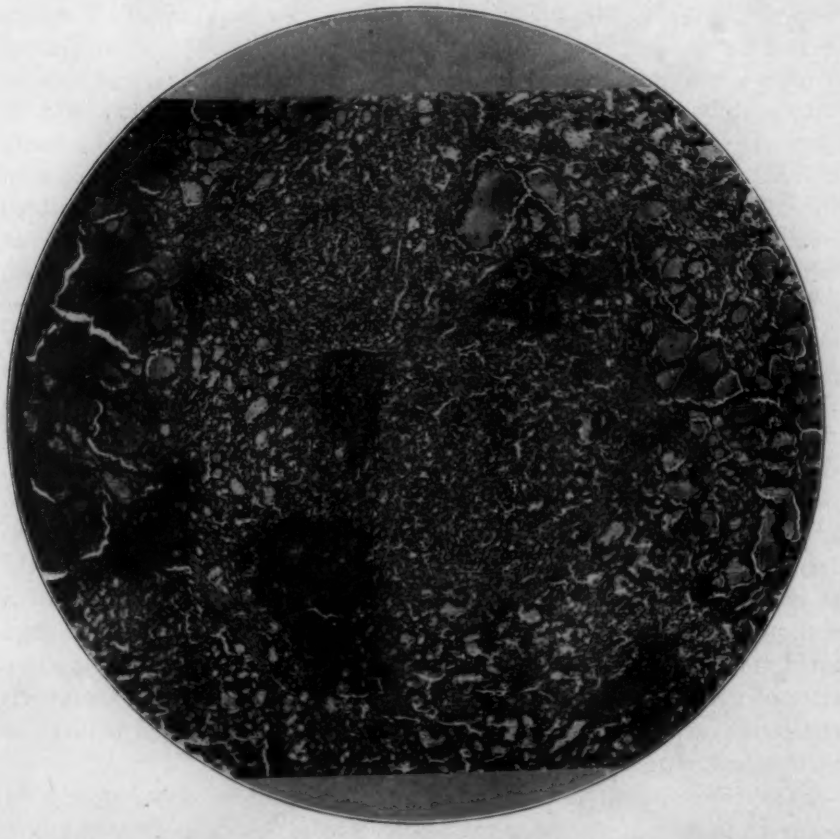

Fig. 18 (case 5).—Section from left lobe of the gland of patient 5 after three weeks' treatment of iodine and a complete clinical remission, showing areas of persistent hyperplasia of three distinct lobules (40 mm. lens); it is noted that the lymphocytes in these areas are pronounced; the adjoining gland can be seen at the periphery to have undergone the normal or average amount of involution occurring throughout the gland, these areas of hyperplasia persisting; from the area in the marked circle figure 19 is made; these areas have been described by various authors as miliary and diffuse adenomas; they are merely areas of persistent hyperplasia.

areas in which the lining epithelium was absent but these areas were probably artefacts. The epithelium was occasionally more flattened and approximated the endothelial type of cell. These cysts contained a large amount of homogeneous, even staining colloid which abutted on the apexes of the epithelial cells. About the periphery of these cysts, there was compressed normal involuted thyroid gland tissue which in general was made up of flattened small acini, intralobular and interlobular sep-

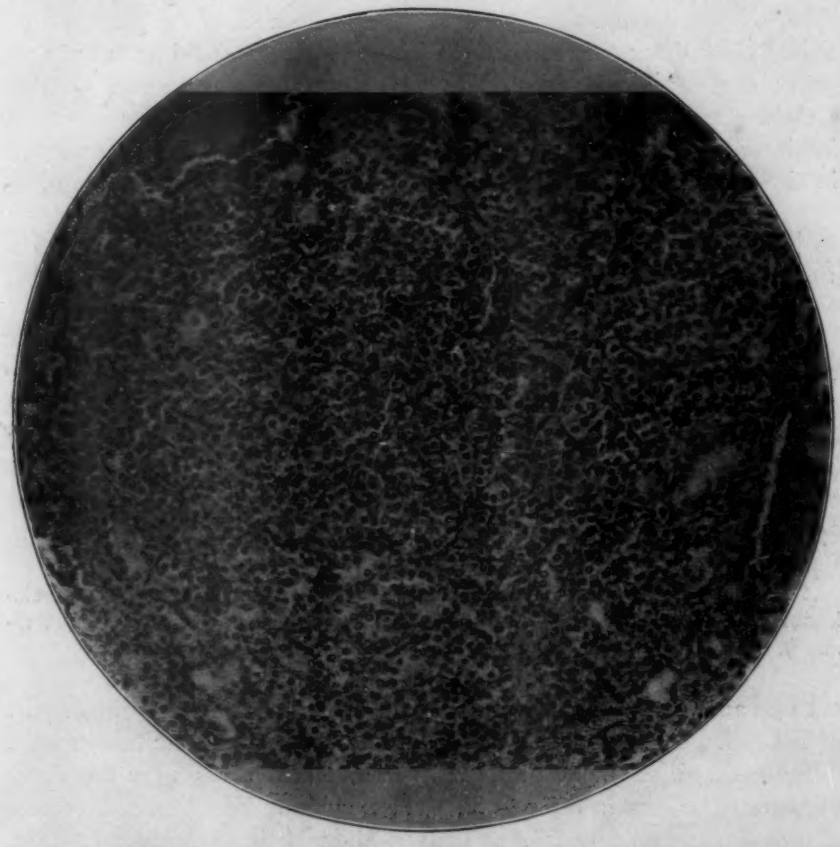

Fig. 19 (case 5).—Area described in figure 18 by circle under higher magnification (×176 mm.); persistent area of hyperplasia with closely packed small acini of the type seen in fetal and infant thyroids is shown; cells lining acini do not show involutionary changes and colloid is striking by its absence.

tums (figs 13 and 17). In these the early stages of actual atrophy and substitution of this parenchyma by connective tissue between the cyst wall and the intralobular septums had not occurred, but it is believed that it would occur if the element of time had been longer, resulting in the formation of a definite connective tissue capsule. The second type of hyperinvolution manifested was in localized areas of very much

dilated acini, filled with colloid and well circumscribed or encapsulated with compressed parenchyma, as well as the interlobular and intralobular septums; these areas were histologically indistinguishable from the so-called colloid adenomas (figs. 5, 8 and 9). These areas were confined to one lobule and were diffusely deposited throughout the entire gland, no sections being entirely free of them, whereas large portions of the same gland, including many sections, removed before iodine was given or before an involution was brought about, showed no areas of this type. These dilated acini were so much larger than the acini of the average glandular tissue about the lobule that they could be seen in the gross (fig. 20) and appeared in all respects similar to the so-called colloid adenomas. The large acini themselves varied quite markedly in size and shape, being larger than the normal acinus but still varying in size with respect to each other. The epithelium was always flattened

Fig. 20.—Gross involutional changes observed to occur following the administration of iodine and during a marked clinical remission of a case of exophthalmic goiter (× 10).

out like an endothelial cell with the nucleus as the most prominent part of the cell. The cytoplasm was scant and the cytoplasmic bodies were difficult to see. In none of these hyperinvoluted areas were there any vacuoles to be seen in the colloid. The involution here caused a regression slightly beyond normal as defined above, being manifested by the size of the acini, the amount of colloid and the extreme flattening and regression of the epithelial cells. It was a very characteristic feature that the interacinous stroma in these areas was quite delicate and thin, and confluence of these acini was not infrequently seen, probably due to the rupture of this delicate stroma at some point, this rupture resulting, no doubt, from nutritive disturbances secondary to the marked distention. The involution of the parenchyma immediately surrounding these areas of hyperinvolution was usually typical of the degree of involution occurring in the gland as a whole (fig. 9). The third type of hyperinvolution observed to develop in this series of cases was one that

far exceeded the normal amount of involution, going on to a state approximating a degeneration of the thyroid parenchyma and usually associated with both of the foregoing types, namely, the cysts and also the areas of hyperinvolution or encapsulated large dilated colloid acini resembling the so-called colloid adenomas. In these areas of extreme involution, one was impressed with the abundance of the material forming the stroma and the paucity of the sparsely situated acini (fig. 15). The acini and their remnants seemed to be literally buried in the large amount of stroma. The latter was composed largely of colloid similar in all respects to that occurring in the acini and was homogeneous and even staining throughout. The stroma was delicate though abundant and seemed to be everywhere filled with this extra-acinous colloid which apparently had escaped into the interacinous areas as a result of the disintegration of the acini. The acini varied in size from that approximating the normal acinus of the thyroid gland down through the smaller grades to small clumps of epithelium consisting of two, three and four cells, grouped in clusters and between which no lumen could be made out. Occasionally, one saw single epithelial cells, while the epithelium as a whole, especially the number of acini, was markedly decreased per lobule in these areas, below the amount present in the normal thyroid gland. The epithelial cells in these areas were low, flat and shrunken, the epithelium was very inactive and seemed to be degenerating in most instances; it was very granular and contained many colloid droplets. The nuclei were markedly shrunken and pyknotic and could often be seen extracellular in the stroma. It is interesting to note that the same type of extreme involutional change is to be found also in the so-called fetal and mixed fetal and colloid adenomas.

AREAS OF HYPO-INVOLUTION

In the other type of involutional bodies which were mentioned, the hypo-involuted areas, it was stated that there were islands or lobules in the glands of exophthalmic goiter which seemed to resist involutional changes or the factors that were efficacious in bringing about the involution of the remainder of the gland. These areas were confined to one lobule, but several such areas were often encountered in one section and, as a rule, seemed to be diffusely scattered throughout the gland. About these areas a localized infiltration of the stroma with small lymphocytes (fig. 18) much more marked than in the remaining portions of the gland, occurred. These areas of hypo-involution were made up of small round acini closely crowded together and containing very small lumina, if any at all (figs. 18 and 19), with the apexes of the cells abutting on each other. There seemed to be such a rapid growth of small acini in the center of the lobule that a great deal of pressure was produced on the peripherally situated parenchyma, against the interlobular

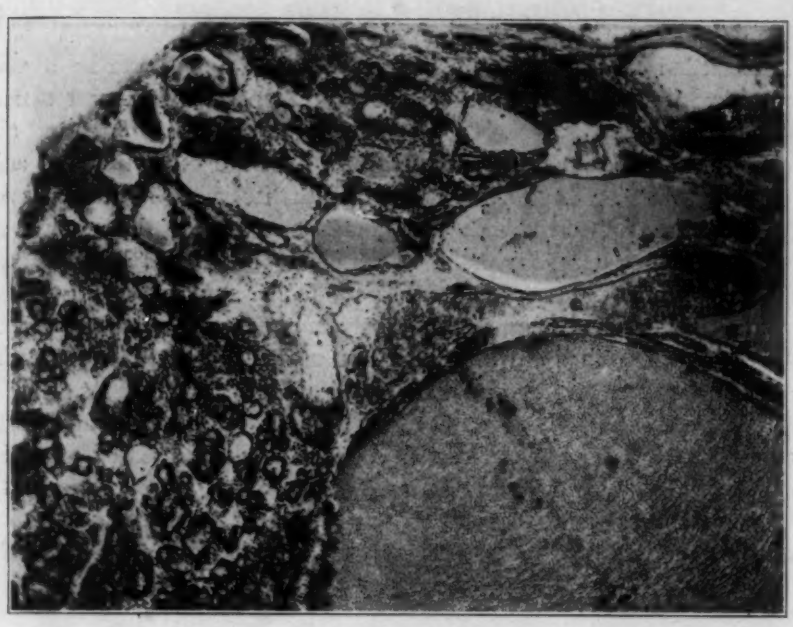

Figure 21

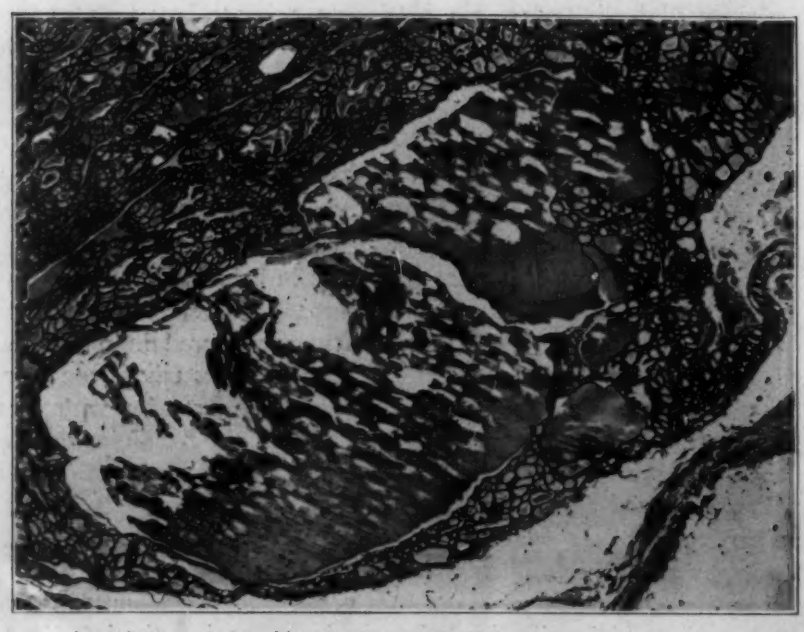

Figure 22

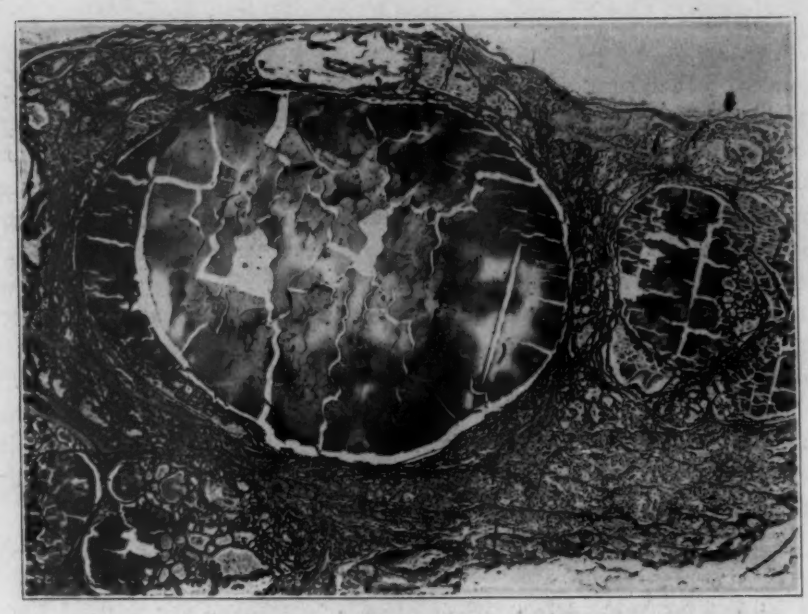

Figure 23

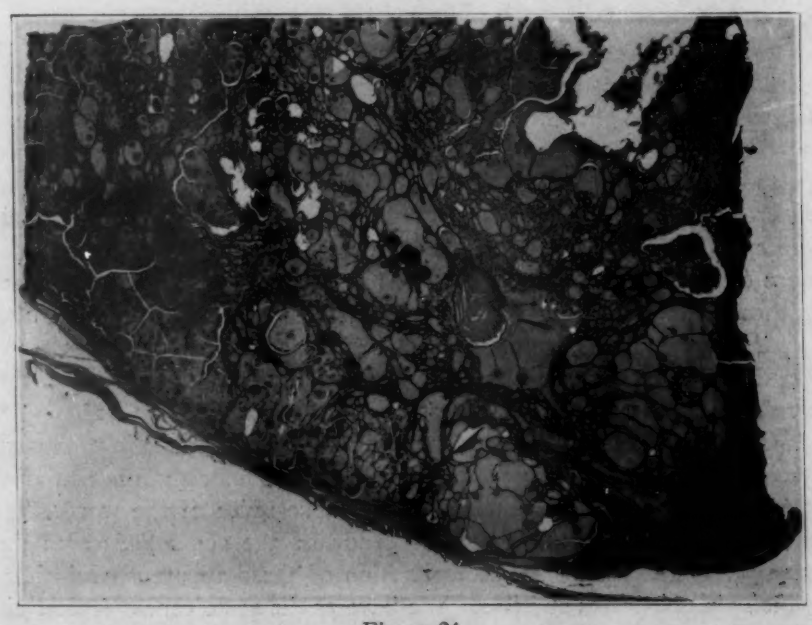

Figure 24

Figs. 21, 22, 23 and 24.—Areas of hyperinvolution that have occurred in the four cases mentioned in the text in the thyroid gland of patients undergoing spontaneous remissions and in which a subsequent exacerbation had occurred when they were removed by operation (× 16); the histologic alterations observed in these cases following a spontaneous involution will be seen to correspond exactly with the involutional changes following an artificial remission or involution.

septums. It did not seem at all clear why these specific areas persisted as centers of active growth while the remainder of the gland underwent involutionary changes throughout, even in the lobules adjacent to those resisting involution (fig. 18). The epithelial cells of the hypo-involuted areas approximated closely the epithelial cell of an active hyperplasia and did not show the involutional changes that were observed in the epithelium in the gland about these areas.

In figure 18 this type of parenchymatous hypertrophy may be seen and represents a well defined encapsulated area of persistent hyperplasia. All that can be said, however, in regard to these areas is that they are localized encapsulated areas of hyperplasia which seemed to resist the involutional changes brought about in the remainder of the gland by the use of iodine. They do not seem to obey the laws governing the remainder of the gland in regard to involution.

SPONTANEOUS INVOLUTION

To demonstrate further the point of involution of the thyroid gland in exophthalmic goiter in figures 21 to 24 are shown microscopic sections from four cases of typical exophthalmic goiters of more than twelve years' standing before operation, and in which unquestionable remissions and exacerbations occurred over six times, including the last exacerbation in each case. After each remission there was noted the appearance of lumps or nodules in the thyroid gland; these nodules increased in size over a period of years. The same involutional changes were observed in these cases that have been noted to have occurred in the seven controlled cases. The lobules containing the large dilated colloid acini and cysts or areas of hyperinvolution were the involutional changes that were established following a previous hypertrophy and hyperplasia and in these instances a secondary hypertrophy had been engrafted on these hyperinvoluted areas or lobules concomitant with the last exacerbation. No doubt another involution would enlarge them still more and they would again become Basedowified in another exacerbation.

Clinically, these patients had typical cases of exophthalmic goiter with the exception of the thyroid gland, which was nodular and felt as though it might be the seat of adenomas, in the true sense of the word. The changes observed in the foregoing study of the controlled cases that have been cited render the interpretation of these apparent clinical and pathologic disparities possible. We have at the same time a typical picture, clinically and histologically, of exophthalmic goiter associated with areas resembling the so-called colloid adenomas but which in truth were not adenomas at all, but merely areas of hyperinvolution following a previous hypertrophy and hyperplasia of the thyroid gland, which had again become involved in the current exacerbation and had again undergone hypertrophy and hyperplasia in sympathy with the remainder of

the gland. To prove further the similarity of the involutional changes observed to occur in the seven cases that were controlled and those occurring spontaneously as well as artificially following an iodine remission, fifty patients with exophthalmic goiter who had received iodine were studied and in all these areas of hyperinvolution occurred accompanying a clinical remission. In five other cases which were refractive to iodine these involutional changes were not observed. From 1900 to 1910, in fifty cases of exophthalmic goiter that had an acute onset and a fulminating course without remission, no involutional changes could be demonstrated in the entire gland, while in fifty cases of exophthalmic goiter in which iodine was not administered but in which there was a history of one or more remissions, these involutional changes were found in great abundance.

COMMENT

In this series of seven cases of exophthalmic goiter the histologic structure of the thyroid gland was studied before and after a clinical remission was established. The clinical improvement and fall in the basal metabolic rate during a remission was accompanied by a transformation in the microscopic appearance of the thyroid gland from that of an extreme hypertrophy and hyperplasia of the parenchyma to that of a resting or colloid state. The resting state of involution was characterized by: (1) increase in the amount of colloid; (2) increase in the connective tissue in the gland; (3) decrease in the vascularity; (4) increase in the size and regularity of the acini; (5) decrease in the height of the epithelium; (6) decrease in the cytoplasmic bodies in the epithelial cells, and (7) decrease in mitosis and lymphocytic infiltration. The latter state was thus shown to be less active, physiologically as well as histologically, than the former state of hypertrophy and hyperplasia. This transformation was called an involution or regression of the hyperplastic thyroid gland in an attempt to reapproximate the histologic structure of the normal thyroid gland. The process of involution is, as a rule, a diffuse one occurring throughout the gland as a whole to about the same degree, except that in certain areas the involution is more or less complete. The average degree of involution observed to occur in this series of seven controlled cases and fifty other cases in which iodine was given has been termed the normal degree of involution occurring during a remission. Involutional changes, more pronounced or in a greater degree as well as in a less degree than normal, were encountered and referred to as areas of hyperinvolution and hypo-involution. The areas of hyperinvolution or involutional bodies were divided into three types: first, the formation of colloid cysts; second, localized and encapsulated areas of dilated colloid acini, histologically indistinguishable from so-called adenomas, and, third, areas or lobules in which

the involution and regression had gone beyond the average or normal amount of involution for that gland to a state of degeneration, characterized by a disparity in the size and paucity of sparsely situated acini in an abundant stroma, which was made up of an increased amount of fibrous tissue and an extra-acinous colloid. Histologically, the areas appeared very similar to the mixed adenomas or fetal and colloid adenomas. No evidence of the formation of new tissue could be made out in these areas and in the latter respect they are again similar to the adenomatous areas named. In the tissue removed before iodine was given no such areas could be found. However, after involution of the gland had occurred these areas of hyperinvolution were abundant. The appearance of these specific areas simultaneous with a remission would seem to indicate that they had their origin in the histologic transformation accompanying involution of the thyroid gland. For this reason they have been termed areas of hyperinvolution. These areas of hyperinvolution were found in this study to be confined usually to one lobule of the thyroid gland, the entire lobule being affected throughout and not only in one portion of a lobule; this fact suggests strongly that the changes observed may have been due to a disturbance either in the lymphatic drainage or in the circulation of the lobule or both. The epithelial elements of these areas showed the most extreme involutional changes and appearance of inactivity. It was pointed out that the localized distention of the acini by the colloid caused a peripheral pressure on the fibrous tissue envelop surrounding the lobule. Evidence of this pressure could be seen by the flattening of the peripherally situated acini against the interlobular septums. Because the arteries in the lobule are, in the main, end arteries and also because of the rapidity with which the involutional changes occur (from ten to fourteen days) there is not time for the adaptation of the circulatory bed of the acinus to this marked stretching and distention. Thus, degenerative changes resulting from circulatory embarrassment due to this stretching and probably occlusion of the smaller branches, at least, are very common, a relative pressure anemia resulting. There were certain lobules, mentioned above, of the thyroid gland in these seven cases of exophthalmic goiter which resisted the factors that were efficacious in bringing about the involutional changes in the remainder of the gland and these lobules have been termed areas of hypo-involution. It was pointed out that the parenchyma surrounding these areas of hyperinvolution and also hypo-involution was always fairly representative of the normal amount of involution occurring throughout the gland as a whole. These areas of persistent hyperplasia were always confined to one lobule and seemed to be, at the same time, areas in which lymphocytic infiltration also persisted and was most marked. They appeared to be histologically similar

to the areas described by Ewing as "miliary adenomata." It was not thought in this study, that any more could be said than that they were areas of persistent hypertrophy and hyperplasia which did not obey the laws governing the involution of the gland as a whole. In the true sense of the word, these areas were not adenomatous for the reason that the structure of the gland was maintained throughout; the general stimulus of hypertrophy and hyperplasia in the gland, as a whole, has been followed in these localized areas or lobules, and there is no evidence of new tissue formation. However, these areas were interesting because they may well serve to explain the temporary beneficial effect or remission following the use of iodine and also why the patient, clinically, cannot be brought to the status of a normal individual by the use of iodine, always being in a state of low grade hyperthyroidism. It is also not felt that the areas of hyperinvolution or persistent colloid bodies are in any sense adenomatous and for the same reasons which are mentioned above, namely, because they maintain the normal histologic structure of the gland; there is no evidence of new tissue formation, and the general stimulus to hypertrophy and hyperplasia of the gland, as a whole, is obeyed in these areas. Cases are shown in this study which have undergone a spontaneous remission and in the glands of which the same type of involutional bodies have been found. Also, in the latter cases, there has been in a subsequent exacerbation, a reinvolvement of these hyperinvoluted areas in the hypertrophy and hyperplasia that has occurred throughout the gland as a whole. It would seem only natural that, given an acinus of normal dimensions which undergoes marked hypertrophy and hyperplasia of the epithelial lining causing it to be folded in on itself with the formation of smaller peripheral acini, would, when ballooned out or distended with a marked deposition of colloid, be much increased in size. When the epithelial lining became infolded, the size of the follicle conformed to the size of the connective tissue capsule surrounding it. But the increased pressure due to the increased amount of colloid causes the filling up of the vesicle to the size of its inner or epithelial lining, thus increasing the size of the acinus, the lobule and ultimately the lobe and entire gland. Subsequent hypertrophies and hyperplasia of the lining epithelium result in another infolding which again becomes ballooned out to a still larger dimension with each involution and so on, ad infinitum, so that a lobule, lobe or even a thyroid gland which is once the site of hyperinvolution actually grows in size with each subsequent hypertrophy and involution. It is very interesting to note that the migrating type or substernal type of exophthalmic goiter is confined entirely to this type of gland which shows signs of previous involutional changes. The consequent growth and actual increase in tissue as a result of these changes forces the gland

into the mediastinum. The acute fulminating cases of exophthalmic goiter as a rule are not substernal.

Fifty cases of exophthalmic goiter in which iodine treatments were given and in which a clinical remission was established were cited and in all of these areas of hyperinvolution occurred. In fifty cases of exophthalmic goiter, from 1900 to 1910, in which the clinical course had been acute and unremitting, no involutional changes or bodies were observed. In five cases that were refractive to iodine, no involutional changes could be demonstrated. In all the cases of exophthalmic goiter in which the history of one or more spontaneous remissions and exacerbations could be obtained these involutional bodies or areas of hyperinvolution were found in abundance. They differed in size throughout the same gland but in the cases that underwent a spontaneous remission they were definitely palpable, clinically, and were noted to enlarge with each exacerbation and remission. There seems to have been a steady enlargement over a period of years in the latter cases, in which steady enlargement was at times accelerated.

If one digresses for the moment from the pathologic hypertrophies and considers the physiologic hypertrophies, interesting problems immediately arise, which of course will have to be investigated in great detail. Involution of the thyroid gland in this series of cases occurred following pathologic hypertrophy and hyperplasia; nevertheless, the histologic changes of involution would in all probability be the same regardless of the cause of the hypertrophy, whether it be physiologic or pathologic, and the microscopic structure and appearance of the thyroid gland as a result of an involution would be constant. So far as it is known, nodular goiter has not occurred in childhood before the onset of the prepuberty and puberty hypertrophy, that is, before 8 or 10 years of age. Following these physiologic hypertrophies involutional changes occur in the same manner as involution occurring after a pathologic hypertrophy. In the female, of course, there is to be added to this the pregnancy plus lactation hypertrophies. The greatest incidence of nodular goiter is between the ages of 12 and 40, or during the period of life in which physiologic hypertrophies most frequently occur. The milder degrees of hypertrophy and hyperplasia are in turn associated with less striking involutional changes, but the same type of involution does occur. In a yet incomplete study, in this clinic, of the available material following physiologic hypertrophies, these areas of hyperinvolution have been by far the greatest factor in producing palpable nodules in the thyroid gland. At present it seems highly probable that the majority of these nodules present in otherwise normal thyroid glands may have had their origin in the involution of a physiologic hypertrophy and are not benign neoplasms or true adenomas but areas of hyperinvolution or involutional bodies. At the present time it cannot be stated

definitely until a careful investigation of the different types of nodular goiter that occur during this period has been made and histologically reclassified. This is being done at the present time, and will be reported later. From the evidence at present, it would seem that most of these tumors palpable in nodular goiters are nothing more than involutional bodies of the same type as have been described above, and that a great many, in fact nearly all of the cases of nodular goiter with or without hyperthyroidism which have been described as colloid adenomas, mixed fetal and colloid adenomas, colloid cysts, cystic adenomas and miliary adenomas are in no sense of the word adenomatous but the result of an attempt on the part of the thyroid gland, following an hyperthrophy, to reapproximate its normal histologic structure, namely, involutional bodies or areas of hyperinvolution and hypo-involution. It is not to be gathered from this article that all nodular goiters are involutional bodies because this is undoubtedly not the case; there are, without question, true parenchymatous adenomas that have been improperly described as fetal adenomas and there also are localized areas of persistent hypertrophy and hyperplasia which have been described as miliary and diffuse adenomas. Whether or not these should be called adenomas is not certain. There are, too, the malignant tumors. Histologically, however, the involutional changes in the thyroid gland are quite as definite as the hypertrophic and hyperplastic changes and should be considered so. The occurrence of the above noted involutional bodies must in the future be taken into consideration and separated in the pathologic classification from true adenomas. For a proper comprehension and interpretation of the pathologic processes which are encountered in a study of the diseases of the thyroid gland, the changes in the microscopic structure during involution and the deposition of these involutional bodies must be taken into consideration.

CONCLUSIONS

1. Associated with a clinical remission, whether artificial or spontaneous, in cases of exophthalmic goiter, involutional changes in the histologic structure of the thyroid gland occur which are just as definite and fundamental as the microscopic alterations occurring during hypertrophy and hyperplasia.

2. These involutional changes may be divided into three different types: (1) normal or average degree of microscopic alteration occurring throughout the gland as a whole; (2) areas of hyperinvolution, and (3) areas of hypo-involution.

3. The normal or average extent of involution occurring in a case of exophthalmic goiter during a clinical remission represents the nearest

return to the normal histologic structure of the thyroid gland that can take place in a gland once the site of an hypertrophy and hyperplasia.

4. The normal or average degree of involution occurring during a remission in this series of seven cases was characterized by: (*a*) increased amount and density of colloid; (*b*) increase in size and regularity of acini; (*c*) increase in amount of connective tissue in the septums and scarring throughout the gland; (*d*) decrease in size and height and change in shape of epithelial cells from a high columnar to a cuboidal or endothelial cell; (*e*) decrease in cytoplasmic bodies or constituents; (*f*) decrease in vascularity of gland, and (*g*) decrease in vacuolization of colloid and deposits of lymphocytes.

5. Areas of hyperinvolution correspond, clinically and histologically, to the so-called colloid adenomas, cystic adenomas, fetal and colloid or mixed adenomas and colloid cysts.

6. The areas of hypo-involution are localized encapsulated areas of persistent hypertrophy and hyperplasia and have been termed miliary adenomas by Ewing and diffuse adenomas by others.

7. Involution of the thyroid gland occurs following hypertrophy and hyperplasia whether this be physiologic or pathologic.

8. These areas of hyperinvolution and hypo-involution are not benign neoplasms of the thyroid gland or adenomas in the true sense but merely residual histologic alterations occurring during an involution of the thyroid gland following an hypertrophy and hyperplasia.

9. These areas of hyperinvolution or involutional bodies may undergo subsequent microscopic alterations denoting hypertrophy and hyperplasia in sympathy with the changes occurring in the gland as a whole. Thus, an increase in their size may occur following each exacerbation and remission.

10. In this study of the seven controlled cases these involutional bodies were directly observed to occur. In fifty cases of exophthalmic goiter undergoing spontaneous remissions and subsequent exacerbations, the same involutional structures were observed in all degrees of development. In fifty cases in which iodine treatment was given areas of hyperinvolution occurred in abundance.

11. The presence of new tissue formation was not found in any of the areas of hyperinvolution.

12. True parenchymatous or fetal adenomas of the thyroid gland do occur but should not be confused with the involutional bodies that are not adenomas.

13. In order properly to interpret the many and bizarre microscopic alterations observed in a study of the diseases of the thyroid gland, a knowledge of the histologic changes occurring during involution is necessary.

THE TRANSPLANTATION OF BONE INTO JOINTS *

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Various attempts to obtain tissue culture of bone have been reported, but thus far there has been no convincing proof or satisfactory demonstration of the growth of bone outside the body. These failures are not surprising when one thinks of the structure of bone with its normal intricate method of growth and repair in response to some physiologic stimulus.

In seeking for a substitute for an artificial culture medium, it was thought that a joint cavity would serve the purpose and act as natural incubator for bone tissue. A joint cavity was selected because it was thought that the synovial fluid would serve as a source of nourishment for young growing cartilage and osteid tissue. It was also expected that the implanted segments of bone would produce a synovitis and that the excess of fluid, as well as the motion of the joint, would tend to keep the pieces of bone moving and prevent them from becoming adherent to the synovial membrane.

It may be well to recall some of the findings of the investigations on the behavior of loose bodies in joints, so far as they have a bearing on the present experiments. Strangeway [1] believes that articular cartilage derives its nutriment from synovial fluid and that loose cartilaginous bodies not only survive in the joint cavities but also may increase in size.

Fisher [2] does not agree entirely with Strangeway that the synovial fluid is the normal source of nourishment for articular cartilage. He asserts that there are two other possibilities; namely, (*a*) plasma extruded from capillaries lying in the cancellous plates abutting on the calcified layer, (*b*) plasma extruded from the plexes of vessels lying beneath the synovia at the margin of the articular cartilage. Fisher believes that cartilage cells, free in a joint, retain their vitality in almost every case and after a time actively proliferate. He states that the majority of bone corpuscles die, as do the contents of the bony spaces. There is never any sign of proliferation of the osteoblasts with the

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1. Strangeway, S. P.: Observation on the Nutrition of Articular Cartilage, Brit. M. J. **1**:661 (May) 1920.

2. Fisher, A. G. T.: A Study of Loose Bodies Composed of Cartilage or of Cartilage and Bone, Occurring in Joints, with Special References to Their Pathology and Etiology, Brit. J. Surg. **8**:493 (April) 1921.

formation of new bone. However, in case there are early adhesions to the synovial membrane there may be a proliferation of osteoblasts and the formation of new bone.

Since the present investigation was started, Ito [3] has reported an interesting result of one of his experiments, in which he placed a segment of bone and cartilage in a joint cavity. He found the specimen free in the joint of a rabbit four weeks after operation. The microscopic examination showed it to be covered by a thin layer of fibrous tissue. The original cartilage had maintained itself, but in certain places the cartilage cells stained feebly and were of lowered vitality. In other places there was some well maintained cartilage proliferation. The old bone tissue had nearly lost its bone cells but slight new bone formation could be seen. The bone marrow consisted mostly of fatty cells and red bone corpuscles.

The negative finding of Fisher, on one hand, and the positive findings of Ito, on the other, leaves the solution of the problem of the growth in free segments of bone in joint cavities still unsettled. In the following investigation, several different principles were utilized which it was thought would help in the successful determination of the question; instead of using a single piece of bone, several fragments were put together, because there is a definite physiologic stimulus for union of several fragments of a transplant, just as there is in the healing of a fracture under normal conditions. Before insertion into the joint, the pieces of bone were placed in a piece of thin perforated rubber tubing to prevent adhesion to the synovial membrane and allow sufficient nutritive material to pass in through the perforations. Young animals were selected because of the greater proliferative power of young osteoid tissue and the piece of bone was obtained from a metacarpal bone or from the upper end of the fibula of the same animal. The following results were obtained in fifteen experiments on dogs and rabbits, all performed under ether anesthesia with aseptic technic.

PROTOCOLS

EXPERIMENT 1 (Dog 62, eight days).—*Operation.*—An incision was made on the outer side of the knee joint of the left leg, and extended inward along the side of the patella to the joint cavity. A second incision was made over the head of the fibula. A section of bone with its periosteum 3 cm. long was removed and broken into a number of fragments. These were placed in two separate pieces of thin rubber tubing tied at both ends and perforated on the sides. Two specimens were then dropped into the joint cavity, after which the wounds were closed in layers.

3. Ito, L. R.: The Nutrition of Articular Cartilage and Its Method of Repair, **12**:31 (July) 1924.

Gross Findings.—The two pieces of tubing were found adherent to the synovial membrane. There were synechia of organized fibrin or ingrowths from the synovial membrane extending into the perforations in the tubing. The bone itself was covered by the same new membrane.

Microscopic Findings.—The bone was surrounded by fibrin. The nuclei throughout the bone stained poorly and there was no sign of proliferation.

EXPERIMENT 2 (Dog 69, nineteen days).—*Operation.*—An incision was made on the outer side of the right knee joint, extending down over the head of the fibula. After the knee joint was opened, a section of bone with periosteum 2 cm. long was removed from the upper end of the fibula. The piece of bone was broken into several fragments which were then placed in a piece of thin rubber tubing tied at both ends and perforated on the sides. The wound was then closed in layers.

Gross Findings.—The tube was found adherent to the tissue just above the patella but was not surrounded by fibrous tissue. The bone appeared dead.

Microscopic Findings.—The greater part of the bone was surrounded by unorganized fibrin. At one end there was some granulation tissue. The nuclei of the bone took a poor stain. There were no signs of proliferation or regeneration at any place. The haversian canals in some places contained red blood corpuscles.

EXPERIMENT 3 (Dog 66, thirty-three days).—*Operation.*—The same procedure was carried out in this experiment as in Experiment 2, with the exception that one portion of fragmented bone was placed in the joint cavity without any covering of rubber tissue.

Gross Findings.—Both specimens were found attached to the synovial membrane in the quadriceps pouch. The specimens appeared viable; the one in the tubing was redder than the other. It looked as though a union of the fragments had taken place in both segments of bone.

Microscopic Findings.—In the pieces of bone that were in the tube many of the nuclei failed to stain. On the periphery there was some new bone, and in one place there was a bridge extending from one segment of bone to another. The bone about the haversian canals stained quite well and within the canals there were new blood vessels. The bone was surrounded by organizing granulation tissue and fibrin. The pieces of bone that were free and not incorporated in rubber tubing stained somewhat better than the other. At one end there was a large mass of cartilaginous callus and osteoid tissue (Fig. 1). The narrow spaces contained fibrous marrow with a considerable number of marrow elements and blood vessels.

EXPERIMENT 4 (Dog 62, thirty-six days).—*Operation.*—A piece of bone 1 cm. long was removed from the upper end of the right fibula and split longitudinally. The two segments were tied together with silk and dropped into the knee joint on the same side.

Gross Findings.—The specimen was found adherent to the synovial membrane at the upper end of the patella. The bone had undergone considerable absorption.

Microscopic Findings.—The piece of bone was encapsulated by fibrous tissue. The greater number of nuclei stained quite well; some, however, took a weak stain. There was no evidence of proliferation; on the contrary, there were signs of absorption on the surface.

EXPERIMENT 5 (Rabbit A (1), thirty-seven days).—*Operation.*—After the joint cavity was exposed, a segment of bone 1 cm. long was removed from a metatarsal bone on the same extremity. This segment of bone was fragmented and after being tied up in rubber tubing was dropped into the joint cavity.

Gross Findings.—The specimen was found attached to the synovial membrane. There was a new tissue extending through the perforation in the tube.

Fig. 1 (Experiment 3, thirty-three days).—Fragments of bone that were dropped into joint and became attached to the synovial membrane; *A*, new osteoid tissue; *C*, new cartilage.

Microscopic Findings.—The original bone took a rather poor stain. Some of the nuclei stained better than others. The marrow space contained some fairly normal looking marrow cells. There was some cancellous bone surrounding the cortical bone that had the structure of new bone but did not take a normal stain.

EXPERIMENT 6 (Dog 65, thirty-seven days).—*Operation.*—The joint cavity was exposed and one set of fragments obtained from the fibula were placed in rubber tubing and another set without tubing were dropped into the joint.

Gross Findings.—Both specimens were found adherent to the synovial membrane in the region of the subpatella fat pad. All the fragments appeared viable and united to one another.

Microscopic Findings.—The two specimens were mixed in the preparation for staining. One of the sections showed actively proliferating bone throughout with a cartilaginous knob at one end. The other showed much less new bone, it being confined to the periphery of the bone. The bone spaces in each contained a thin reticulum, rich in blood vessels.

EXPERIMENT 7 (Dog 63, forty days).—*Operation.*—A section was removed from a metatarsal bone, broken into six pieces and after being placed in rubber tubing was inserted into the left knee joint.

Gross Findings.—The tubing was attached in the region of the subpatella fat pad, and a pannus of tissue extended through the perforations. All the fragments except one appeared to be viable.

Microscopic Findings.—The majority of the fragments appeared to be united by new osteoid tissue (Figs. 2 and 3). Part of these fragments were composed of well stained tissue like regenerated bone, while other portions contained poorly stained nuclei. There were some separate fragments that were made up mostly of degenerated nuclei, only a portion on the periphery taking the nuclei stain. The marrow spaces of the major portion of the specimen were filled with a vascular fibrous marrow.

EXPERIMENT 8 (Dog 64, forty-two days).—*Operation.*—A piece of bone was removed from the femur and broken into several fragments, after which it was placed in a piece of tubing and inserted into the knee joint. The dog opened the wound on the eighth day.

Gross Findings.—The joint cavity was filled with clear synovial fluid. The tube was slightly adherent to the synovial membrane at one place. The bone appeared dead.

Microscopic Findings.—There was practically a complete failure of staining of the nuclei of the bone.

EXPERIMENT 9 (Rabbit A (2), fifty-six days).—*Operation.*—A segment of bone was removed from the metatarsal bone and after being tied in rubber tubing was inserted into the left knee joint.

Gross Findings.—The rubber tubing was found adherent to the synovial membrane. The bone appeared viable.

Microscopic Findings.—There was a large amount of cartilaginous and osseous callus connecting the fragments of bone. The nuclei of the original bone for the greater part were stainless; only those about the periphery and the haversian canals stained. The marrow spaces contained in part normal marrow cells, and in some places fat and fibrous tissue.

EXPERIMENT 10 (Dog 63, sixty-eight days).—*Operation.*—Several fragments of bone obtained from the metatarsal bone were placed in rubber tubing and dropped in the joint cavity of the right knee.

Gross Findings.—The specimen was found attached in the region of the subpatella fat pad. The bone had undergone considerable absorption.

Microscopic Findings.—The bone was well stained throughout and it appeared as though the fragments had united and that regeneration was complete. There were a number of giant cells on the surface and evidence of absorption.

EXPERIMENT 11 (Dog 65, seventy-two days).—*Operation.*—A small piece of bone, the periosteum of which was partly detached, was removed from the upper

Fig. 2 (Experiment 7, forty days).—Fragments of bone were placed in perforated rubber tubing and dropped into the knee joint. The tubing was found attached to the synovial membrane and the contained fragments were united by osteid callus. *A-A,* original bone, showing poor staining of nuclei; *C,* new osteoid callus connecting the two fragments.

end of the right fibula. The bone was fragmented and after being placed in rubber tubing was inserted into the knee joint.

Gross Findings.—The tube was found attached on the side of the quadriceps pouch. The bone had undergone marked atrophy but appeared viable.

Microscopic Findings.—The remnant of bone was encapsulated by connective tissue. Most of the nuclei stained normally. The bone was evidently undergoing absorption, and there was no evidences of proliferation.

EXPERIMENT 12 (Dog 67, eighty days).—*Operation.*—A piece of bone 3 cm. long was removed from the left fibula and after being broken into a number of fragments was placed in rubber tubing and inserted into the knee joint of the same side.

Gross Findings.—The specimen was found attached to the joint lining. The fragments of bone appeared alive and it looked as though they were united.

Microscopic Findings.—There was a definite union of all the fragments. In the original bone the nuclei about the haversian canals and on the periphery

Fig. 3 (Experiment 7, forty days).—Area *A-C* shown in Figure 2 under higher magnification; *A-A*, poor staining of original bone; *C-C*, new well stained osteoid callus extending to another fragment of bone.

stained well, while some on the interior failed to stain. There was new osseous callus connecting the various fragments, and in some places it was still cartilaginous. The bone spaces contained vascular fibrous marrow.

EXPERIMENT 13 (Dog 66, eighty-eight days).—*Operation.*—A piece of bone 3 cm. long with periosteum and endosteum was removed from the upper end of the right fibula; this was fragmented and after being put in a rubber tubing was inserted into the knee joint of the same side.

Gross Findings.—The specimen was found attached in the region of the quadriceps pouch. One small piece was found in the rubber tubing and another piece was outside the tube, both having undergone considerable absorption.

Microscopic Findings.—The larger piece of the specimen was composed of two types of bone, one that appeared to be undergoing degeneration and absorption

and another that was proliferating. The marrow spaces contained both fibrous and lymphoid marrow. The smaller piece of bone contained only a few well stained nuclei and was evidently undergoing absorption.

EXPERIMENT 14 (Dog 67, one hundred and eight days).—*Operation.*—Two specimens of fragmented bone from the right fibula, after being placed in rubber tubing, were inserted into the knee joint.

Gross Findings.—Only a small fibrous nodule was found.

Microscopic Findings.—No bone was found in the section.

SUMMARY

1. In these experiments in which pieces of bone enclosed in rubber tubing were inserted into a joint, well stained or new bone was found in practically every case in which a sufficient time had elapsed. The cycle and the character of the changes were similar to those which took place in a transplanted piece of bone under normal conditions. The processes were slower, less active, and there was a tendency for earlier degeneration.

2. In some of the experiments, cartilaginous and osteoid callus was found uniting the fragments. The ultimate fate after restoration was complete absorption, as with other transplants in a nonfunctioning position.

3. After insertion in the joint cavity, the specimens more than likely remained free for several days. At eight days one was found attached to the synovial membrane, but was surrounded by unorganized fibrin. At nineteen days there was beginning organization at the place of attachment; therefore, it seems justifiable to conclude that for the period previous to this time, the fragments were able to subsist on nutrient material obtained from the synovial fluid. We should bear in mind that the fragments were enclosed in perforated rubber tubing and thereby received only a limited supply of necessary food elements; it was therefore all the more remarkable that the fragments were not only able to survive but to form callus in sufficient amount to have united the pieces of bone.

4. The foreign bodies excited no inflammatory reaction on the part of the synovial membrane, and no changes took place in the articular cartilages.

5. In every experiment the tube with its enclosed contents became adherent to the synovial membrane, thereby defeating the primary purpose of this investigation, but the results are nevertheless interesting and important. It is hoped that methods may be devised by which the fragments may be kept free in the joint cavity, or for the successful cultivation of bone outside the body.

CONCLUSIONS

1. Bone fragments placed in perforated rubber tubing and inserted into a joint remained viable and were able to produce sufficient new bone to form a union between the fragments.

2. The foreign bodies caused no injury to the articular cartilage and always became adherent to the synovial membrane.

TUBERCULOSIS OF THE MAMMARY GLAND*

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The education of the public to look on any mass in the breast as a potentially serious condition is leading to more satisfactory treatment of the neoplastic lesions of this organ. Granted, however, that every mass in the breast is to be considered malignant by the laity until proved otherwise, the physician must be able, within reasonable limits, to differentiate between the benign and the malignant new growths. Certainly tuberculosis of the breast holds a definite place among the benign conditions of this organ which must be differentiated from the malignant. The number of cases, however, remain small as compared with the number of cases of neoplasm and no one group of cases of mammary tuberculosis has been large enough in itself to allow of general statements or definite conclusions. The number of cases proved by microscopic examination and completely reported in the literature probably is now sufficient, when reviewed as a whole, to allow fairly accurate deductions.

Before the advent of microscopic section methods of examining tissues there were many who doubted the existence of tuberculous mammary gland disease, some being so bold as to state that this was the one organ exempt from this infection. Among these stood Virchow. Cooper [1] described the condition in 1829 but his experience, like that of many of the earlier observers, was limited to the more advanced and more evident type or stage of the disease, that is, cases in which well developed cold abscesses were present or those in which sinus formation had already taken place. The frequency with which less extensive forms and earlier stages of the disease are being reported is due as much, no doubt, to the education of the laity to look on any mass in the breast with grave suspicion as to the improved diagnostic methods. Greater attention must be given, then, to the differential diagnosis of early stages of tuberculosis of the breast in order to suspect such a condition.

There are certain classical notions regarding mammary gland tuberculosis, some of which are not entirely correct in view of the entire series of reported proved cases. Among these accepted statements are: (1) that the condition is rare; (2) that the disease early takes the form of abscesses and sinuses; (3) that axillary and cervical gland tuberculosis often precede the breast condition and the latter results from a

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1. Cooper, Astley: Illustrations of Diseases of the Breast, London, 1829.

lymphatic extension from these primary foci; (4) that gland involvement occurs during the period of sex activity; (5) that the process is practically always unilateral; (6) that the right breast is more frequently attacked than the left; (7) that the breast lesion is associated with other foci of tuberculous infection and therefore is secondary; (8) that previous mammary infection and trauma are common predisposing causes; (9) that breast tuberculosis is always of the bovine type.

The statement that breast tuberculosis is a clinical rarity is supported by the relatively few cases reported. However, one must not overlook the fact that since attention has been directed to the condition, reports are becoming more frequent. Delbet [2] in 1891 was able to compile only thirty-six cases while Gauthier [3] in 1895 compiled seventy-nine cases, forty-three of which were proved tuberculosis by microscopic examination. Scudder [4] in 1898 reported eighty-three compiled cases and in the following year Carrel [5] increased the number to 120, although all of them were not proved by microscopic examination. Pataroni [6] in 1907 and Durante [7] in 1914 compiled and reported sufficient cases to bring the number to 150. In 1914 Deaver [8] reviewed the literature and compiled the cases in the period from 1904 to 1914. With the five cases he had observed himself he was able to report seventy-seven cases in which a diagnosis had been definitely established. Since 1914 fifty cases have been reported and I am permitted to add fifteen cases compiled from the Department of Surgery at the University of Michigan Hospital.

Five of the seven cases reported by Raw [9] were not proved tuberculosis, either by finding the tubercle bacilli or by tissue examination. Of these five cases it is quite likely that one at least was not mammary tuberculosis, but rather a cold abscess beneath the breast and secondary to tuberculosis of the shoulder joint. If we disregard the unproved cases there have been forty-five cases reported which with the additional fifteen reported herewith bring the total number reported since 1914 to sixty cases.

Although only fifteen cases can be reported from the University Hospital, it is interesting to note that the Department of Pathology files show a total of fifty-two cases of mammary tuberculosis from all

2. Delbet, quoted by Chauvin, E.: Comité méd. des Briches du Rhone, Nov. 17, 1922; Arch. franco-belges de chir. **26,** 1923; Progrès méd. **38**:109 (March 10) 1923.
3. Gauthier: Thèse de Bordeaux, 1895.
4. Scudder: Am. J. M. Sc. **116**:75, 1898.
5. Carrel: Gaz. d. hôp., 1899, p. 1945.
6. Pataroni: Thèse de Bordeaux, no. 126, 1907.
7. Durante: Policlinico **21**:139, 1914.
8. Deaver: Am. J. M. Sc. **147**:157, 1914.
9. Raw, N.: Brit. M. J. **1**:657 (April 12) 1924.

sources, or one case to each forty-five of malignancy. This evidence compares closely with the statement of Scott [10] that there is one case of tuberculosis of the breast to fifty of cancer.

The commonly accepted opinion that the disease as seen clinically is usually in the stage of abscess and sinuses is not entirely correct. A review of the compiled cases shows that only thirty-seven of 140 cases showed sinus formation when the patients first presented themselves for examination. In only eight cases of forty-eight was a diagnosis of abscess made by clinical examination. To be sure, caseation and small abscess formation are found in a much larger proportion of cases by microscopic examination. There is undoubtedly a group of cases in which evolution is very slow and these with a smaller group that present the gross picture of infiltrating granulation tissue make up the majority of the cases. The latter sclerosing type of the disease has been very aptly called the "tuberculous pseudoneoplasm" by Chauvin.[11] The disease takes this peculiar form, no doubt, because of the low virulence of the organism or the greater resistance of the host. In this form spread to the axillary glands may be early and here the process may go on rapidly to caseation even though the primary breast lesion remains small and of the noncaseating type.

Contrary to the once accepted opinion mammary tuberculosis is not commonly due to spread of the infection from cervical and axillary glands. Raw [9] stresses the secondary involvement of the breast from extensive cervical and axillary tuberculosis in five of his cases. Extension to the breast does take place in this way but much less frequently than was formerly thought. Less than half the compiled cases show any cervical or axillary involvement and a large number of the patients presenting palpable axillary glands give a definite history of having observed the enlargement of the nodes after the appearance of the mass in the breast. Not more than 5 per cent of the cases of tuberculosis of the breast arise as extensions from axillary or cervical tuberculous glands.

Only five cases of bilateral mammary gland tuberculosis have been reported, one case each by Albertin,[12] Walther,[13] Bonneau,[14] Durante and McCarty [15] and Chauvin.[11] The disease can be considered as almost universally unilateral. There is no evidence to support the conclusion that there is a gross predilection for one breast over the other. Of 122 cases, sixty-two involved the right breast and sixty the left breast.

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10. Scott: St. Bartholomew's Hosp. Rep. **40**:97, 1904.
11. Chauvin (footnote 2).
12. Albertin, quoted by Chauvin (footnote 2).
13. Walthier: Bull. et mem. Soc. d'anat. de Paris **32**:1076, 1906.
14. Bonneau: Société des chirurgiens de Paris, Oct. 15, 1920.
15. Durante, L., and McCarty, W. C.: Ann. Surg. **63**:668 (June) 1916.

Secondary involvement of the breast from a tuberculous focus elsewhere is much less common than was thought by early observers. The more usual locations for primary foci, when present, are cervical and axillary glands and the lungs. The earlier writers on the subject considered mammary tuberculosis to be secondary to pulmonary infection in all cases. At present there is a tendency to an almost complete reversal of this opinion. The truth lies in a middle ground. Scott [10] in reporting twenty-seven cases found no case of pulmonary tuberculosis. In the group of sixty cases reported since 1914 (including the fifteen reported at this time) eighteen patients showed tuberculosis or gave a history of having had a definitely diagnosed tuberculous lesion elsewhere than the breast. Of these eighteen patients ten had pulmonary tuberculosis. Chauvin [11] places the association of the breast condition with a pulmonary infection at 12 per cent while the foregoing analysis would put the incidence at 16.6 per cent.

Trauma and previous chronic inflammation of the breast have been considered important predisposing factors. Trauma is given as a definite cause in but two cases of forty-eight and previous chronic inflammation of the breast was present in only 10 per cent of the cases. Although trauma cannot be considered a causative factor, frequently here, as in benign growths of the breast, an injury will lead to the discovery of the condition. Four cases of tuberculosis of the breast associated with benign neoplasms have been reported by Walther,[15] Schley,[16] Massabuan [17] and Bundschuk.[18]

All cases in which the type of bacillus has been determined have proved to be bovine in type, but the number of cases from which the bacilli have been cultured is much too small to warrant conclusions. The difference in the rapidity of caseation in various cases may be explained by the type of infection. It is known that elsewhere in the body the bovine infection more often runs a chronic course than does the human bacillus infection.

Attempts have been made to classify tuberculosis of the breast as disseminated or confluent but the increasing number of cases that cannot be forced into such a grouping has led to the adoption of a classification on a quite different basis. If, indeed, a classification is necessary, the following seems to answer the present needs:

Primary:

1. Breast tuberculosis with rapid evolution.
2. Breast tuberculosis with slow evolution.
3. Sclerosing type (tuberculous pseudoneoplasm).

Secondary:

Tuberculosis of breast from glandular origin; rapid evolution.

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16. Schley: St. Lukes Hosp. Rep., 1910, p. 1147.
17. Massabuan: Montpel. méd. **28**:608, 1909.
18. Bundschuk: Beitr. z. path. Anat. u. z. allg. Pathol. **57**:65, 1913.

The more common form of the disease is that of a localized mammary gland lesion, without demonstrable focus elsewhere, with or without spread to the axillary nodes. The process here, if not interrupted by treatment, goes through three stages: nodule, abscess and sinus. The rapidity with which the change takes place varies and the subdivision of the primary group is made on this basis of rapidity of evolution of the process. Every stage is possible. Caseation may take place early with abscess and fistula formation simulating subacute mastitis or the process may be of the sclerosing type that remains for several years without breaking down.

DIAGNOSIS

The lump in the breast is insidious in its onset and usually free from pain until distention of the tissues by a considerable mass occurs or the overlying skin is involved. In twenty-three of forty-eight reported cases there was slight or severe pain at the time of the first examination but in only two had pain been an early symptom. Early abscess and sinus formation takes place in the secondary and rapidly evoluting primary types (usually within two to four months). These two groups, when taken together, make up less than 20 per cent of the cases. Diagnosis in these cases is usually evident and it is not surprising that before laboratory methods of diagnosis were available these were the only known types.

The slowly caseating type along with the sclerosing form make up a most interesting clinical entity. It is this group in which diagnosis is most difficult. It is not uncommon for these patients to give a history of a lump in the breast for several years. Remissions followed by an increase in size of the mass with pregnancies or menses occur in some cases. One case (case 1) of our series gave such a history with remissions and exacerbations extending over a period of eight years. Four of the patients had first noticed the lump more than a year before admission and in none had the first symptoms appeared less than five months before the patient came for examination. In none of the cases had sinus formation occurred. Axillary gland involvement is usually relatively early, but it is of no value in differential diagnosis. Fixation and dimpling of the skin and retraction of the nipple may be present. In a case reported by Miles [19] and another by Hartman and d'Allaines [20] retraction of the nipple was the first indication of a lesion. Discharge

19. Miles: Edinburgh M. J. **14**:205, 1915.

20. Hartmann, Henri; and d'Allaines, G.: Bull. Soc. d'obst. et de gynéc. de Paris, 1924, no. 6.

Reported by	Year	Sex*	Age	Social	Children	Side Involved	Fistula or Sinus	Duration of Symptoms	Size	Location in Breast	Pain	Condition of Skin	Nipple: Retraction	Nipple: Discharge
Miles [19]														
1.....	1915	♀	49	S	..	R	.....	.....	Hen's egg	Lower half	With appearance of swelling	Not adherent	First symptom	Milky white
2.....	1915	♀	36	M	9	R	+	Several weeks	Large lump	Central	+	Dark blue over swelling	+	.....
3.....	1915	♀	47	M	10	L	+ 2	About (?) 2 weeks	Large mass to axilla	Upper outer	None	Bluish about sinuses	+	.....
4.....	1915	♀	29	M	2	L	.....	.....	.....	Upper inner	Not stated	Not stated	Not stated	Not stated
5.....	1915	♀	35	M	2	L	+	6 weeks	5 by 3 in.	Upper outer	+	Bluish movable edges about sinuses	+	Not stated
6.....	1915	♀	23	S	..	R	.....	4 months	Orange	Near nipple	No	Not adherent	Not stated	Not stated
Gatewood [22]														
1.....	1916	♀	36	M	1	R	+ several	4 years	2 cm. in diameter	Upper inner	Slight	Not stated	+	+
2.....	1916	♀	26	S	..	R	+	7 months	3 cm. when first noted	Not stated	No	Not stated	Not stated	Not stated
3.....	1916	♀	37	M	6	R	With healing 3 +	18 years	At largest 4 cm.	Below nipple	During menses	Reddened	Not stated	Not stated
4.....	1916	♀	48	M	6	L	Following incision	Indefinite period	6 cm.	Upper inner	Slight	Numerous old scars	Not stated	Not stated
5.....	1916	♂	44	..	..	L	.....	6 months	Not stated	Outer	No	Not stated	Not stated	Not stated
Durante and McCarty [16]														
1.....	1916	♂	52	..	..	L	Single abscess	.....	.....	Lower	Not stated	Slight inflammation	No	Not stated
2.....	1916	♀	28	..	..	L	.....	.....	.....	Upper outer	+	Not involved	No	Not stated
3.....	1916	♀	23	..	..	L	Single abscess	.....	.....	Lower outer	Slight	Slight inflammation	No	.....
4.....	1916	♀	27	..	..	L	.....	.....	.....	Upper outer	Slight	Not involved	No	.....
5.....	1916	♀	40	..	..	R	.....	.....	.....	Upper outer	Slight	Not involved	+	.....
6.....	1916	♀	26	..	..	R & L	.....	.....	.....	Upper inner and upper outer	Slight	Not involved	No	.....
7.....	1916	♀	22	..	..	L	+	.....	.....	Nipple region	Slight	Not involved	No	.....
8.....	1916	♀	41	..	..	L	+ 1	.....	.....	Upper exterior	Slight	Ulcerated	No	.....
9.....	1916	♀	28	..	..	R	.....	.....	.....	Generalized	Slight	Not involved	+	.....
10.....	1916	♀	42	..	..	R	.....	.....	.....	Generalized	Slight	Not involved	No	.....
Hamilton [23]														
1.....	1920	♀	44	..	..	R	.....	.....	.....	Not given	.....	.....	.....	.....
Cheever [24]														
1.....	1921	♀	37	M	..	L	.....	7 months	.....	Upper outer	Stabbing pain	.....	+	.....
2.....	1921	♀	23	M	..	L	+ 3	6 months	.....	Lower central	Slight +	Ulcer	.....	.....
3.....	1921	♀	21	S	..	L	.....	Not given	Mass	Not given	.....	Not involved	.....	.....
4.....	1921	♀	36	M	..	Not given	After inc.	7 weeks	Mass	Not given	Tenderness	Sinus	.....	.....
Archibald [25]														
1.....	1922	♀	40	M	1	L	.....	16 months	.....	Not given	+	.....	+	.....
Elkin [26]														
1.....	1923	♀	36	..	..	R	+	Not given	.....	Upper inner	.....	Sinuses	.....	.....
2.....	1923	♀	21	..	..	L	+	Not given	.....	Lower outer	.....	Sinus	.....	.....
3.....	1923	♀	26	..	Yes	R	.....	Not given	.....	Lower	....	Not given	.....	.....

* In this table, ♂ indicates male; ♀, female.

22. Gatewood: Mammary Tuberculosis, J. A. M. A. **67**: 1660 (Dec. 2) 1916.
23. Hamilton, E. P.: Surg. Gynec. Obst. **30**: 567 (June) 1920.

Palpable Axillary Gland	Initial Symptoms	Previous Condition of Breast	General Physical Examination	General Health	Heredity	Treatment	Result	Microscopic Diagnosis	Tuberculosis Found	Animal Inoculation
.....	Retraction of nipple	Normal	Amputation right leg, tuberculosis knee	Good	Tuberculosis in family	Excision of breast	Satisfactory	Plus	.....	.....
.....	Lump	Abscess 3 years before	Negative	Good	Negative history	Partial excision of breast	Discharged practically healed	.....	.....	.....
+	Lump	Normal	Negative	Good	Negative history	Partial excision of breast and axillary glands	Satisfactory	.....	.....	.....
.....	Abscess	Incision and drainage; abscess 2 weeks; healed	Negative	Good	One sister died of tuberculosis	Incision and drainage	Slow healing	.....	.....	.....
Single nodule	Pain and lump	Retracted nipple	Negative	Fair	Negative history	Excision of breast and axillary glands	Uneventful recovery	Plus	.....	.....
No	Lump	Normal	Negative	Good	Negative history	Excision of portion of breast	Healed	Plus	.....	.....
No	Lump	.....	Negative	Excellent	Negative history	Abscess and sinuses removed	Primary closure	Plus	.....	.....
Not stated	Lump, 3 cm.	Normal	Pulmonary tuberculosis	Good	Negative history	Partial breast excision	Healed	Plus	.....	.....
+	Lump	Injured 18 years before; abscess, swelling and pain	Negative	Good	Negative history	Excision of breast	Primary healing	Plus	.....	.....
+	Lump	Numerous incisions and drainage of abscesses	Negative	Good	Negative history	Excision of breast	Not stated	Plus	.....	.....
Operation previously	Swelling	Normal	Lost 20 pounds (9 Kg.) in 1 year	Fair	Negative history	Excision of outer half of breast	Not stated	Plus	.....	.....
Not stated	.....	Not given	Tuberculosis of lungs; left empyema	Poor	Negative history	Not stated	Not stated	Plus	.....	.....
No	Single nodule	Not given	Tuberculosis of lungs	Poor	Negative history	Not stated	Not stated	Plus	.....	.....
No	.....	Not given	Tuberculosis of lungs	Poor	Tuberculosis in family	Not stated	Not stated	Plus	.....	.....
No	Nodular; multiple	Not given	Tuberculosis of lungs	Poor	Tuberculosis in family	Not stated	Not stated	Plus	.....	.....
No	Single nodule	.....	Negative	Good	Negative history	Not stated	Not stated	Plus	.....	.....
Both axillary glands	Nodular; multiple	.....	Tuberculosis of lungs	Poor	Negative history	Not stated	Not stated	Plus	Plus	.....
Both; neck	Cyst	.....	Negative	Good	Negative history	Not stated	Not stated	Plus	.....	.....
No	.....	.....	Negative	Good	Negative history	Not stated	Not stated	Plus	Plus	.....
Right axillary; both cervical	Diffuse sclerosis	.....	Negative	Excellent	Negative history	Not stated	Not stated	Plus	Plus	.....
Right axillary	Diffuse sclerosis	.....	Appendix and right adnexa removed; 2 years	Poor	Negative history	Not stated	Not stated	Plus	Plus	.....
+	.....	.....	Pulmonary	Not stated	Not stated	Excision of breast and axillary glands	Healed	Plus	.....	.....
.....	Lump	.....	Negative	Good	Negative history	Partial excision of breast and axillary	Not stated	Plus	.....	.....
.....	Mass	.....	Negative	Good	Negative history	Amputation of breast, gland dissection and roentgen-ray treatment	Not stated	Plus	.....	.....
.....	Mass	Negative	Negative	Good	Not stated	Partial excision of breast	Healed	Plus	.....	.....
.....	Tender mass	Negative	Negative	Good	Not stated	Excision of breast	Healed	Plus	.....	.....
.....	Painful mass subsided; returned in 3 mo.	After 12 months	Negative	Good	.....	Excision of breast and part of axillary gland	.....	Plus	.....	.....
+	.....	Negative	Negative	Good	.....	Amputation of breast	Healed 5 years	Plus	.....	.....
.....	.....	History of trauma	Negative	.....	.....	Breast amputation	Healed 1 year	Plus	.....	.....
.....	.....	Negative	Negative	Good	.....	Partial excision of breast	Healed 2 years	Plus	.....	.....

24. Cheever, D.: Surg. Clin. N. Amer. 1 : 919 (June) 1921.
25. Archibald, R. G.: Ann. Trop. Med. 16 : 225 (Oct.) 1922.
26. Elkin: Ann. Surg. 77 : 661 (June) 1923.

Reported by	Year	Sex*	Age	Social	Children	Side Involved	Fistula or Sinus	Duration of Symptoms	Size	Location in Breast	Pain	Condition of Skin	Nipple: Retraction	Nipple: Discharge
4.....	1923	♀	24	..	..	L	.....	Not given	.....	Lower inner	.....	Not given	.....	.....
5.....	1923	♀	23	..	Yes	L	+	Not given	.....	Lower inner	.....	Sinus	.....	.....
6.....	1923	♀	37	..	At time of onset	L	+	Not given	.....	Upper outer	.....	Sinus	.....	.....
7.....	1923	♀	34	..	Yes	R	+	Not given	.....	Central	.....	Sinus	.....	.....
Chauvin														
1.....	1923	♀	38	M	1	L	Abscess	1 month	Nut	Nipple and outside of nipple	.....	Adherent later	.....	.....
2.....	1923	♀	25	M	..	L	Axilla	Very long	.....	Superior external	+	Adherent	.....	.....
3.....	1923	♀	..	M	8	R & L	.....	16 days	.....	Superior external	+	.....	.....	.....
Raw														
1.....	1924	♀	17	S	..	Not given	After drainage	Few weeks	.....	.....	.....	Sinus	.....	.....
2.....	1924	♀	37	..	..	R	+	1 year	.....	.....	.....	Sinuses	.....	.....
3.....	1924	♀	19	..	..	R		Not given	.....	.....	.....	Sinuses	.....	.....
4.....	1924	♀	33	..	..	R	+	6 years	Massive	.....	.....	Sinuses	.....	.....
5.....	1924	♂	27	..	..	L	.....	.....	.....	.....	.....	.....	.....	.....
6.....	1924	♂	23	..	..	L	.....	.....	.....	Upper	.....	.....	.....	.....
7.....	1924	♂	22	..	..	R	.....	2 months	.....	.....	+	.....	.....	.....
Hartmann and d'Allaines [20]														
1.....	1924	♀	49	M	..	Not given	.....	.....	.....	Central	.....	Reddened; fixed to mass	+	.....
2.....	1924	♀	59	M	..	R	.....	3 weeks	Small	.....	+	Adherent	.....	.....
3.....	1924	♀	25	M	1 miscellaneous	Not given	.....	18 months	4 nodules	Upper outer	.....	Slightly reddened; slightly adherent	+	.....
4.....	1924	♀	24	M	2	R	.....	1 year	Mass	Inner upper	+	Reddened	+	+
University Hospital														
1.....10/19/17		♀	30	M	3, 1 miscellaneous	R	After incision and drainage	8 years at intervals	Hen's egg	Outer	+	Sinuses	+	+
2..... 5/ 1/19		♀	38	M	..	R	.....	18 months	Small	Inner outer	+	.....	.....	.....
3..... 7/18/22		♀	47	M	6	R	.....	9 months	Pigeon's egg	Center	.....	.....	.....	.....
4.....12/ 4/22		♀	43	M	..	R	.....	5 months	Mass	.....	+	.....	.....	.....
5..... 1/26/25		♀	47	M	12	L	.....	16 months	3 by 5 in.	Upper outer	.....	.....	Slight	.....
6.....	..	♀	40	M	5	R & L	.....	7 weeks	Small mass	Central	+	.....	Slight on left	.....
7.....	..	♀	29	M	2	R	.....	6 months	Large mass	Outer	Slight	.....	.....	.....
8.....11/22/12		♀	34	M	3	L	.....	17 months	Mass subsided and reappeared	Outer	Slight	.....	.....	.....
9.....	..	♀	50	M	4	L	.....	.....	Hen's egg	Outer	Slight	.....	.....	.....
10.....	..	♀	22	S	..	R	.....	5 months	Cherry	Upper outer	.....	.....	.....	.....
11.....	..	♀	27	M	..	L	.....	5 months	Lump	Above nipple	.....	.....	+	.....
12.....	..	♀	32	M	4	R	.....	14 years	Hickory-nut	Upper outer	Present 1 year	Scar	+	.....
13.....	..	♀	36	M	2	R	.....	.....	Lump	Upper	.....	.....	.....	.....
14.....	..	♀	22	M	..	L	.....	8 months	Mass	Lower	Slight	Fixed	.....	.....
15.....	..	♀	29	M	3	R	.....	6 months	Mass	.....	Slight	.....	+	.....

* In this table, ♂ indicates male; ♀, female.

Cases—Continued

Palpable Axillary Gland	Initial Symptoms	Previous Condition of Breast	General Physical Examination	General Health	Heredity	Treatment	Result	Microscopic Diagnosis	Tuberculosis Found	Animal Inoculation
+	.....	Negative	Tuberculosis of rib	.....	Tuberculosis in family	Excision of sinus and rib	Healed 5 years	Plus	.....	.....
+	.....	Negative	Negative	.....	Negative history	Breast amputation; dissection of axilla	Well, 18 months	Plus	.....	.....
.....	.....	Negative	Negative	.....	Negative history	Partial breast amputation	Well, 3 months	Plus	.....	.....
.....	.....	Negative	Tuberculosis of lung	.....	Negative history	Breast amputation	Well, 5 months	Plus	.....	.....
.....	Nodule	Negative	Negative	Good	Negative history	Partial excision of breast	Healed 1 year	Plus	.....	Plus
+	Small nodules	.....	Suspected tuberculosis	Fair	Negative history	Partial breast amputation and axillary dissection	Healed	Plus	.....	.....
+	Mass	.....	Lung	Poor	Negative history	Amputation of breast and axillary dissection	Healed	Plus	.....	.....
Cervical; axillary	Mass	Negative	External cervical tuberculosis	.....	.....	Drainage of abscess	Healed, 10 months	.....	Bovine	.....
Axillary; cervical	Mass	Negative	External cervical and axillary	.....	.....	None	Not known	.....	Bovine	.....
Axillary; cervical	.....	Negative	External tuberculosis of gland	.....	.....	Sinuses scraped	Healed, 16 months	.....	.....	.....
Cervical	Mass	.....	External cervical tuberculosis	.....	.....	Sinuses scraped	Healed, 14 months	.....	.....	.....
.....	.....	Tuberculosis of axillary glands; shoulder	.....	.....	.....	.....	.....	.....	.....	.....
Cervical and axillary	Mass	Negative	.....	.....	.....	Of cervical and axillary sinuses	Breast subsided	.....	.....	.....
.....	Mass fluctuation	.....	Tuberculosis of knee, ankle and tibia	....	....	General hygienic	.....	Not proved tuberculosis	.....	.....
One axilla	Retraction of nipple	Negative	Negative	Good	Negative history	Amputation of breast, axillary dissection	Healed, 1 year	Plus	.....	.....
Axilla +	Pain nodule	Negative	Negative	Good	Tuberculous history	Breast amputation; axillary dissection	Healed, 9 years	Plus	.....	.....
Axilla and supra-axilla	Nodule	Negative	Negative	Good	Negative history	Radical breast amputation	Healed	Plus	.....	.....
Axilla	Discharge from nipple	Negative	Negative	Good	Negative history	Incision and drainage of abscess	Healed	.....	.....	Tuberculosis found
Axilla	Swelling and pain	Negative	Negative	Fair	Negative history	Breast amputation; axillary dissection	Healed	Plus	.....	.....
Axilla	Mass	Negative	Negative	Good	Negative history	Incision and drainage	Wound draining when discharged	Plus	.....	.....
.....	Mass	Negative	Negative	Poor	Negative history	Radical breast amputation	Healed	Plus	.....	.....
.....	Pain and mass	Negative	Enlarged spleen	Good	Negative history	Radical breast amputation	Healed	Plus	.....	.....
.....	Mass	Abscess 16 years before	Negative	Fair	Husband had tuberculosis	Local excision of masses; later, breast amputation	Healed	Plus	.....	.....
.....	Pain	Negative	Negative	Good	Negative history	Radical breast amputation	Healed	Plus	.....	.....
+	Mass	Negative	Negative	Good	Negative history	Amputation of breast	Healed	Plus	.....	.....
.....	Mass and pain	Negative	Negative	Good	Negative history	Amputation of breast	Healed	Plus	.....	.....
.....	Mass	Negative	Negative	Good	Negative history	Partial excision of breast	Healed	Plus	.....	.....
.....	Mass	Negative	Negative	Good	Negative history	Local excision of mass	Healed	Plus	.....	.....
.....	Retraction of nipple	Negative	Negative	Good	Negative history	Amputation of breast	Healed	Plus	.....	.....
.....	Mass	Mass 14 years	Negative	Fair	Negative history	Amputation of breast	Healed	Plus	.....	.....
+	Mass	Negative	Negative	Good	Negative history	Amputation of breast	Healed	Plus	.....	.....
.....	Mass	Negative	Negative	Fair	.....	Local excision of mass	Healed	Plus	.....	.....
.....	Mass	Negative	Negative	Good	Negative history	Amputation of breast	Healed	Plus	.....	.....

from the nipple is an uncommon finding but attracted attention to the condition in a case observed by Hartman and d'Allaines.[20] Pain was the primary symptom in five of forty-eight cases.

On palpating the breast it is found that the slowly evoluting forms do not present a well defined border as do the more rapidly caseating types, here again presenting the characteristic findings of a scirrhous carcinoma. Large portions or the entire breast may be involved with a diffuse sclerosis, making the involved breast more prominent and firmer than normal.

The age of the patient (tuberculosis of the breast occurs more often in younger persons than does cancer) along with a history of remissions can only suggest the correct diagnosis. Confirmation must always come from tissue examination.

TREATMENT

Opinion unanimously favors surgical treatment. If there is a well localized lesion in the breast this may be removed along with a margin of normal tissue; if the process is more extensive, the entire breast must be removed along with the axillary glands when definitely involved. It is not necessary to take as wide a margin of skin as in cancer and the pectoral muscles can be saved in the majority of cases. Removal of the outer portion of the pectoralis major may be necessary in order more easily to attack the axilla. Primary healing is the rule, recurrence uncommon.

With more conservative treatment such as the medical treatment as advocated by Von Eberts,[21] the results are quite unsatisfactory. More conservative operative measures, such as draining of abscesses and curettement of sinus tracts and iodoform gauze dressings, have given local healing but only after months of treatment. Recurrence after the more consecutive forms of treatment is much more common.

CONCLUSIONS

1. Tuberculosis of the breast occurs in the proportion of 1:40 as compared with cancer of the breast and 1:20 with other chronic inflammations of the breast.

2. In the majority of cases, no other tuberculous lesions can be found.

3. Sclerosing and slowly evoluting types are clinically difficult to diagnose and can only be suspected.

4. Local excision of the lesion or breast amputation with removal of the axillary glands, if these are palpable, is the treatment of choice.

5. The pectoralis muscles can be preserved in the majority of cases.

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21. Von Eberts: Am. J. M. Sc. **138**:70, 1909.

THIRTIETH REPORT OF PROGRESS IN ORTHOPEDIC SURGERY*

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CONGENITAL CONDITIONS

Congenital Dislocation of the Patella.—Zanoli [1] gives an interesting study of congenital dislocations of the patella. He has observed and studied thirteen patients, forming a total of sixteen cases. The cases may be divided into two classes, permanent dislocations and habitual dislocations. He has made a study of the literature and discusses it and also various operations that have been devised. His article is illustrated by excellent photographs and roentgenograms. As regards etiology, heredity seemed frequently to be a factor. There was also a familial factor, since he noted in the literature one instance in which three sisters had the same deformity. Sex played no part. The pathology is obscure, but his conclusion is that congenital dislocation of the patella is due to an abnormal orientation of the articular axes and more precisely to an external rotation of the tibia and an inward torsion of the distal epiphysis of the femur. Certainly the essential cause is some intrauterine mechanical factor. He discusses the various methods of treatment that have been employed. In his series of cases various methods were used, and in regard to them he says, "I believe I do not err in asserting that the methods which merit a greater appreciation and a larger application are medial transplantation of the patellar tendon and capsulorraphy, which can, with much advantage, be combined."

Congenital Elevation of the Scapula.—Schrock [2] states that in an embryo of five weeks the scapula becomes differentiated opposite the fourth, fifth and sixth cervical vertebrae; at the ninth week the scapula begins to descend from the neck to the thorax. Failure to descend gives

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* This Report of Progress is based on a review of 186 articles selected from 412 titles dealing with orthopedic surgery appearing in medical literature between Dec. 12, 1925, and March 13, 1926. Only papers that seem to represent progress have been selected for note and comment.

1. Zanoli, R.: Chir. d. org. di movimento **10**:83 (Dec.) 1925.
2. Schrock, R. D.: J. Bone & Joint Surg. **8**:207 (Jan.) 1926.

rise to the deformity. This failure may be due to maldevelopment in bone, cartilage and muscle, or the descent may be interrupted by abnormal pressure or position in utero. He describes a very radical procedure that has given good results in two severe cases. He believes that the complete correction of the bony deformity often necessitates such operation. The incision is curved from the midsuprascapular region from about 1 inch (2.5 cm.) external to the medial margin of the scapula to 2 inches (5 cm.) below the inferior angle. The deeper incision is carried through the cartilaginous medial margin of the scapula with subperiosteal removal of the combined attachments of rhomboids, serratus magnus and subscapularis. The subscapularis is completely removed. Similar subperiosteal elevation is made of the infraspinatus, teres major and minor, completely freeing the inferior angle and lower two thirds of the axillary border. The same procedure is applied to the insertion of the trapezius on the spine, to the supraspinatus, and to the structures of the superior margin of the scapula, using special care at the suprascapular notch. This is the only point at which there is danger to nerve or vessel of any consequence. The chondro-osseous bridge from the vertebrae to the superomedial margin of the scapula is removed as completely as possible; the margins of the scapula are freely removed; the supraspinatus portion is resected and much of the spine, if this is at all prominent. If the shoulder then cannot be brought back freely, an osteotomy of the base of the acromion is done. This gives a very appreciable downward and backward drop of the shoulder. One strut of the shoulder suspension has in this way been removed. The inferior angle of the scapula is anchored with heavy chromic catgut to the lowest rib possible. The dressing is with a pressure pad over the shoulder and long adhesive extending well down on to the trunk. This is a very important detail, and considerable downward and backward pressure can be applied in this manner. Over this is placed a figure-of-eight of the shoulders, such as is commonly used in fracture of the clavicle.

[ED. NOTE.—In our experience operations for the relief of congenital elevation of the scapula have often somewhat improved the condition, but never either cosmetically or functionally represented complete correction. This is certainly a very radical and extensive procedure that Schrock proposes and the end-results that he presents in roentgenograms and photographs are extremely good.]

RICKETS; BONE DISEASE OF UNCERTAIN ORIGIN

Experimental Rickets.—Buschke and Peiser [3] have fed rats a substance called thallium, with establishment of the bone changes recog-

3. Buschke and Peiser, N.: Klin. Wchnschr. **3**, 1925.

nized as rickets as it appears in rats, also the checking of growth and development, disturbance of sexual function, loss of hair, cataracts and stomach changes. Buschke and Peiser believe that thallium acts as a poison to the endocrine glands and the nervous system and that as a conclusion it seems probable that rickets is produced in the same way in human beings, i. e., that poor hygienic conditions and poor nutrition produce endocrine gland disturbance with rickets as a result.

Coxa Vara.—Noble and Hauser [4] have grouped seventy-five cases of coxa vara, dividing them into fifty-eight adolescent and seventeen congenital, believing that coxa vara may be so grouped. Of the fifty-eight adolescent patients, forty-two were males and sixteen females; the origin of the disease was probably some embryonic vascular disturbance of the femoral neck. In its mildest form this deformity begins at the fourth year and steadily progresses with growth. Roentgenograms will frequently show a fissure in the femoral neck in these cases. The adolescent type of coxa vara is generally seen in the obese or pituitary type of person and is noticed as a rule at the age of puberty when the adiposity is greatest. The authors believe that the pituitary gland plays an important rôle in coxa vara, trauma exerting only a minor influence.

Epiphyseal Coxa Vara.—Key [5] reports twenty-four cases of coxa vara and discusses at length the pathology of this condition. He believes that the true pathology is not known because no early specimen has been studied. He discusses the various theories as to etiology, and concludes that a weakness of unknown origin takes place in the periosteum which binds the head to the neck of the femur. This weakness develops at the period of most rapid bone growth. Key's review is a most extensive and exhaustive one.

[Ed. Note.—We would suggest that as various clinical entities become defined we adopt more descriptive terms. For instance, the etiology of adolescent coxa vara is still in question, but the pathology of the condition is well known and represents a displacement of the upper epiphysis of the femur. It represents a clinical entity, and as such should be differentiated from other types of coxa vara. We would suggest the term "epiphysolysis" to designate the condition.]

Von Recklinghausen's Bone Disease.—Guillain [6] calls attention to the fact that two symptoms characterized the case reported by him of von Recklinghausen's disease. Extreme pain was present as the bone tumor

4. Noble, T. P., and Hauser, E. D.: Acute Bone Atrophy, Arch. Surg. **12**:501 (Feb.) 1926.

5. Key, J. A.: J. Bone & Joint Surg. **8**:53 (Jan.) 1926.

6. Guillain, G.: Bull. et mém. Soc. méd. d. hôp. de Paris **49**:1607 (Dec. 18) 1925.

developed, disappearing afterward, and there was increased local temperature over the affected areas of bone.

Bone Lesions in von Recklinghausen's Disease.—Babonneix, Touraine and Pollet [7] describe the deformities in certain cases of osteitis fibrosa hyperplastica as that of kyphoscoliosis so marked in character that the third lumbar body was seen in profile in an anteroposterior roentgenogram of the spine. The profile skull plate showed a hypertrophy of the bone but no change in the sella turcica. Microscopically and macroscopically the bone lesions were those of osteomalacia.

Gaucher's Disease, Showing Bone Disintegration and Joint Involvement.—Cushing and Stout [8] report a case of Gaucher's disease in which there was marked destruction of the head and neck of the femur. There were also large collections of spleen cells (Gaucher's cells) in the bone marrow of the femoral head and neck, which were apparently the cause of the bone destruction. Gaucher's disease is a primary idiopathic hypertrophy of the spleen, with anemia, bronzing of the skin, and bleeding of the gums.

POLIOMYELITIS

The time interval between infantile paralysis cases in 253 families has been studied by Aycock and Eaton.[9] The period of incubation in man varies from ten to eighteen days, averaging fourteen days. It was inferred that the time of greatest infectiousness of infantile paralysis is probably at the beginning or within the first three or four days of the acute stage of the disease. This study suggests that the search for the source of infection should be centered at about the fourteenth day before the onset of acute symptoms. Making a comparative study of measles, they point out that secondary cases of measles usually occur from ten to twelve days after the onset of the initial case in the family, and that third cases occur, as a rule, simultaneously with the second cases. Infantile paralysis when introduced into a family acts quite differently from measles or scarlet fever. Only exceptionally do multiple cases occur. When multiple cases do occur, it is usually within a short time of each other, indicating simultaneous infection. The virus of infantile paralysis enters the family in such a way that in a few instances in which more than one member is affected, this is accomplished practically simultaneously.

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7. Babonneix, L.; Touraine, and Pollet, L.: Bull. et mém. Soc. méd. d. hôp. de Paris **49**:1601 (Dec. 18) 1925.

8. Cushing, E. H., and Stout, A. P.: Gaucher's Disease, Arch. Surg. **12**:539 (Feb.) 1926.

9. Aycock, G. F., and Eaton, P.: Am. J. Hygiene **5**:724 (Nov.) 1925.

Bulbar Poliomyelitis.—McEachern [10] reports six cases of what he calls epidemic bulbar poliomyelitis. All cases presented the common clinical symptom of paralysis of the muscles of the upper respiratory tract without coincident paralysis elsewhere. In several cases there was a white frothy mucus in the nose and throat. All patients were very ill and two died. The constant involvement of the muscles supplied by the eleventh nerve was unusual.

Gill,[11] in reviewing the symptomatology of various epidemics of poliomyelitis, found that rigidity of the neck was a symptom in 80 per cent of the cases. This is not a voluntary rigidity.

Boehm [12] discusses those cases of infantile paralysis in which most of the muscles of the leg are paralyzed and weight bearing therefore very difficult or even impossible. Boehm does not favor arthrodesis of the knee or hip in children and believes that the most important factor is proper statics. A good artificial leg allows proper weight bearing without muscular action. The paralyzed leg may also be fitted for weight bearing if the statics are correct. Any contracture of the knee or the hip must be corrected. An osteotomy in one or more places will accomplish this and the effect is what he calls a passive security. A line is drawn from the center of the hip to the front of the ankle joint. The trochanter and especially the knee must lie behind that line. Ordinarily the osteotomy is best performed above the knee, but this depends on the kind of deformity.

TUBERCULOSIS

Arthrodesis of the Sacro-Iliac Joint for Tuberculosis; Study of End-Results.—Smith-Petersen and Rogers [13] report the present results in thirteen cases of sacro-iliac tuberculosis in which operations were performed after the method of Smith-Petersen in the last seven years. With careful examination to localize the lesion, with a well planned and correctly executed operation and with proper after-care, this lesion may thus be successfully treated. Of the thirteen patients nine are now well. There was no operative mortality. Four died of tuberculosis elsewhere in the body after periods of one and a half to two years.

[ED. NOTE.—In view of the poor prognosis that is generally assigned to this condition in textbooks, the high percentage of successful results here reported seems to us to represent real progress in the treatment of tuberculosis of the sacro-iliac joint.]

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10. McEachern, John: Epidemic Bulbar Poliomyelitis, J. A. M. A. **86**:90 (Jan. 9) 1926.

11. Gill, J. M.: Brit. M. J. **1**:232 (Feb. 6) 1926.

12. Boehm, M.: Deutsche med. Wchnschr. **51**:942 (June 5); 987 (June 12) 1925.

13. Smith-Petersen, M. N., and Rogers, W. A.: Arthrodesis for Tuberculosis of Sacro-Iliac Joint; Study of End-Results, J. A. M. A. **86**:26 (Jan. 2) 1926.

Resection of the Knee for Tuberculosis in Adults.—Fredet [14] reports twenty-seven cases, of which three of the patients were from 17 to 19 years, twenty were from 21 to 36, one was 51, and another 61. Of these twenty-seven patients he saw eight after four years or longer. The time at which he saw the others varied from three years to six months after operation. He obtained ankylosis in good position in all cases. Function was good in all cases, and the greatest amount of shortening was 5.5 cm. In these cases Fredet has used a metal suture to secure bony apposition without inconvenience in the majority of cases.

Iodized Oil in the Treatment of Surgical Tuberculosis.—Delbet [15] reports the results of treatment by the Finikoff method, using iodized vegetable oil. The cases reported were treated under the personal direction of Finikoff and were fourteen in number; the injections were given throughout a period of from six to eight months, at five to seven day intervals. The first injection contained 10 cc. of the oil, the following 20 cc. The injections were given at points distant from the lesion. Calcium chloride was given at the same time by mouth. In cases of tuberculous abscess, multiple fistulas and tuberculous arthritis, he reports clinical cures and what seemed inevitable amputation was averted in several of these. The basic idea of the treatment known as Finikoff's is to increase the lipolytic power of the mononuclear cells, at the same time increasing the proteolytic power of the polymorphonuclear cells.

[Ed. Note.—There are so many pitfalls to accurate observation in the estimation of results of therapy that we feel that a much larger series of cases will have to be reported before an expression of opinion is possible on Finikoff's method. To anyone attracted to the method, we would suggest the necessity of proving tuberculosis present before reporting on its cure.]

ARTHRITIS

The Orthopedic Aspects of Chronic Arthritis.—Osgood,[16] in the Hugh Owen Thomas Lecture of 1925, reviews the orthopedic aspects of chronic arthritis, discussing the classification, the theories of etiology and the methods of treatment. He believes that many types of organisms and many other factors enter into the etiology of the so-called proliferative infectious or rheumatoid arthritis, Ely's type I. Complete recovery in the early stages may occur if these factors can be eliminated. In later stages arrest of the disease and functional improvement may be attained. The simple surgical removal of a focus of infection will rarely be successful in checking the progress if subsequent attention is

14. Fredet, Pierre: Bull. et mém. Soc. nat. de chir. **52**:43 (Jan. 23) 1926.
15. Delbet, P.: Bull. Acad. de méd. **94**:1083 (Dec. 1) 1925.
16. Osgood, R. B.: J. Bone and Joint Surg. **8**:1 (Jan.) 1926.

not paid to normal bodily mechanics and the principles of better general health. The degenerative, hypertrophic form or ostearthritis, Ely's type II, may often be present without any demonstrable cause. In its early stages if a faulty body chemistry and a faulty bodily mechanics can be corrected and intra-articular friction can be eliminated, almost complete relief from its symptoms is possible. Later, intelligent physiotherapy, protective apparatus and proper orthopedic surgery will be beneficial.

Chronic Arthritis and Diabetes.—Pemberton noted that patients with chronic arthritis seemed to improve when they were given diets low in carbohydrates and were made worse by diets high in carbohydrate. From this he concluded that patients with diabetes should be comparatively free from arthritis, because of the fact that their disturbed metabolism of sugar demanded prolonged diets low in carbohydrates. Schmitt and Adams [17] observed during the last year at the Mayo Clinic 474 patients with diabetes. Fifty-one of these (10.8 per cent), who had well defined but as a rule comparatively mild diabetes, had arthritis. No noticeable improvement in arthritic symptoms occurred in consequence of the low carbohydrate regimen necessary in the presence of diabetes.

[ED. NOTE.—Although Pemberton did not differentiate between the two main types of chronic arthritis, the authors state that most of their cases were of the hypertrophic type, usually situated in the joints of the spine. They do not state how long it had existed before the diabetic diet was begun, but presumably for many years. Such a diet would in our opinion be expected to exert little favorable influence on this type II hypertrophic or ostearthritic senile form. In fact, it might well by its high protein content aggravate it.]

The Dangers of Protein Therapy.—Treatment with protein bodies is administered to such an extent in chronic disease of the joints that it is timely for Zimmer and Buschmann [18] to warn us against certain dangers in this treatment. Such dangers are the anaphylactic shock, serum disease and chronic protein poisoning. Intravenous injection is more dangerous than intramuscular injection. The injection should not be repeated at too short intervals. Changing the substance to be injected, slowly increasing the quantity, and gradual or divided injection are measures of safety. In order to avoid chronic protein poisoning, treatment should not be administered for more than four or six weeks without intermission.

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17. Schmitt, E. O. G., and Adams, S. F.: Association Between Diabetes Mellitus and Chronic Infectious Arthritis, J. A. M. A. **86**:535 (Feb. 20) 1926.

18. Zimmer and Buschmann: Ztschr. f. ärtzl. Fortbild. **22**:513, 1925.

Spondylitis and Spotted Fever.—Holst [19] reports his extensive experience with spondylitis following spotted and recurrent fever. He has seen fifty-six cases. The affection begins with very sudden and rapidly increasing pain, which generally decreases even without treatment. Occasionally traumatism marks the beginning. The pain frequently radiates downward. Contracture of the legs, paresis and even paralysis may ensue, and deformities of the spine, such as kyphosis or scoliosis. In most of his cases the lumbar vertebrae were affected. The roentgenogram showed a narrowing of the intervertebral disk, changes of the vertebra itself, and the formation of bony bridging osteophytes. In some cases a complete union of two vertebrae had taken place. The clinical picture as well as the roentgenogram corresponded closely to that of spondylitis following typhoid fever, but was very different from tuberculous disease of the spine. The disease consists evidently in an osteomyelitic process which soon passes the bony limits and affects the cartilage and the perivertebral tissue. The process is generally benign and the prognosis is good. The treatment is simple and consists of rest in bed in the prone position.

BONE AND JOINT SURGERY

Ganglions.—Kuettner and Hertel [20] regard a ganglion as a neoplasm originating from the primitive connective tissue cells from which the joint develops. Since there is a symmetrical bilateral distribution of the tumors in 3 per cent of the cases they believe that hereditary factors play a certain part. Ganglion of the wrist is most frequent, about 80 per cent of all cases, and of these 70 per cent are seen in females of from 10 to 25 years of age who use their wrists very actively, as in piano playing or similar occupations. Ganglion of the knee or of the foot is most frequent among men after the thirtieth year. Traumatism may favor the development of the tumor, but is not considered the cause. The suggestion that tuberculosis plays a part, as is claimed by certain French writers, is not proved according to the authors. A ganglion of the flexor tendons of the fingers may produce the picture of "snapping" or "trigger finger." The differential diagnosis between a ganglion and a bursitis may be quite difficult. Spontaneous healing has been observed in about 16 per cent of the cases. Treatment may be by crushing, by subcutaneous incision and evacuation, or by complete excision. Even with the latter method, recurrence is seen in about 30 per cent of the cases.

End-Results of Treatment of Joint Wounds by Early Mobilization.—Willems [21] has recently reexamined a number of patients with old joint

19. Von Holst, L.: Ztschr. f. orthop. Chir. **46**:321, 1925.
20. Kuettner, H., and Hertel, E.: Ergebn. d. Chir. u. Orthop. **18**:377, 1925.
21. Willems, C.: Bull. de l'Acad. roy. de méd. **5**:284, 1925.

injury from gunshot wounds, which he had treated seven or eight years previously by his well known method of immediate active mobilization. He describes the ultimate results in fifteen cases of wounds of the knee and in five cases of wounds of the elbow. Most of the wounds were the result of shell explosions and in five there had been purulent arthritis. In the latter group numerous osteophytes have developed, but in none do they interfere with function. He describes the musculature as excellent in these as well as in all other cases, and he feels that the end-results bear out all his claims for the benefits of the method.

Behavior of Sequestrums in Chronic Osteomyelitis.—Van Dessel [22] has made a series of experiments on rabbits which show that in the presence of infection completely separated sequestrums never unite to the newly formed involucrum or to the old bone. The zone of demarcation between the sequestrum and the involucrum, dead or alive, persists until the sequestrum completely disappears either by expulsion or absorption.

Bone Grafting of the Mandible.—Billington and Round [23] have made a report of their experience in the treatment of 2,000 cases of wounds of the jaws and face. Of these a large percentage were compound fractures of the mandible. In these the goal was to obtain osseous union, with accurate occlusion of the teeth, and at the same time avoid disfigurement. If the loss of bone was less than one-half inch (1.2 cm.) the attempt was usually made to secure contact of the fragments at the sacrifice of bony length; if more than one-half inch, it was considered necessary to employ a bone graft. In all, seventy-five patients were successfully treated by bone grafts, the defect varying from one-half inch to 5 inches (12.7 cm.). The longest graft used was 7 inches (17.7 cm.). Some of their observations are as follows: The mandible is peculiarly intolerant of foreign bodies such as wire, pegs or plates. Dovetailing of the grafts did not prove a successful method. The usefulness of the pedicle bone graft was very limited and free grafts were used almost entirely. They employed bone from various sites, but finally concluded that the ribs were too soft, the tibia too hard and too liable to necrosis, and that the best material for transplantation was the crest of the ilium which was tough and could be shaped. Splints were not used until after the wound had healed; if used earlier they caused necrosis. Their procedure was as follows: 1. Operation was not performed until all mouth sinuses were healed and all sepsis eliminated. 2. No splints were used until two weeks after the operation. 3. The operation ought not to open into the mouth, and if this accident occurred the operation was

22. Van Dessel, Arthur: J. Bone & Joint Surg., January, 1926, p. 194.

23. Billington, William, and Round, Harold: Brit. J. Surg. **13**:497 (Jan.) 1926.

abandoned. 4. The graft was taken from the crest of the ilium, and the ends bevelled to fit over the bevelled ends of the mandibular fragments. It was placed with enough overlap to allow for future widening of the jaw with splints. 5. Firm bony union was usually obtained in from two to four months. 6. Prosthetic apparatus was not fitted until the end of six months.

Dupuytren's Contracture.—Under the title of Hereditary Contraction of the Palmar Fascia, Apert [24] reports observation of a family with Dupuytren's contraction in four generations. It affected males only, and in each successive generation it appeared at a slightly earlier age. The possibility of lead poisoning had been eliminated and thus an hereditary predisposition seemed to be the sole cause. One of the cases was treated by the application of radium emanations to the palm of the hand on five successive nights. The result was excellent; the contracted fascial bands relaxed, leaving only a cord, which does not interfere with the use of the hand.

Surgical Exposure of the Entire Radius.—Henry [25] describes an anterolateral incision by means of which the radius may be exposed throughout its entire length. With the hand supinated and the elbow extended, a straight incision is made extending from a point at the outer edge of the biceps belly to the tip of the radial styloid. Then the biceps tendon is exposed and the finger inserted in the muscular groove to the outer side of this tendon and passed distally to the elbow until the recurrent vascular loop is encountered. This should be ligated and divided. Then the three long muscles at the outer border of the forearm are mobilized. The tendon of the brachioradialis is detached. The elbow should be flexed 90 degrees and the supinator muscle exposed, turning it outward with the posterior interosseous nerve. The hand is pronated and the entire radius revolves into view.

Snapping or Trigger Finger.—Kroh [26] has made a careful study of fourteen cases of so-called "snapping" or "trigger" finger, and concludes that the cause is a stenosing tendovaginitis of the flexor tendons of the fingers. The lesion has its seat not at the region of the interphalangeal joint, as is commonly supposed, but at the level of the metacarpophalangeal joint, where the tendon sheath is physiologically narrowed by the ligamenta accessoria volaria. The snapping may occur in flexion or in extension, or in both movements. It may be caused by various changes, such as a circumscribed thickening of the tendon while the sheath is intact, or by a thickening of the sheath while the tendon is unaltered. In the latter case there may be pain on movement

24. Apert, E.: Bull. et mém. Soc. méd. d. hôp. de Paris **49**:1502, 1925.
25. Henry, A. K.: Brit. J. Surg. **13**:506 (Jan.) 1926.
26. Kroh, F. R.: Arch. f. klin. Chir. **136**:240, 1925.

without the phenomenon of snapping. The treatment consists in the excision of the volar part of that section of the tendon sheath which interferes with movement of the tendon. Histologic examination of the tissues removed at operation showed hyperplasia of all the elements of the sheath, and if the condition was advanced there was noted laceration and vascularization of the ligaments and even hyaline degeneration. There was never any increase in the amount of fluid in the sheath, but rather a little dryness.

Arthrodesis of the Sacro-Iliac Joint for Arthritis, Traumatic or Nontraumatic.—Smith-Petersen and Rogers [27] have made a careful and detailed study of a group of cases diagnosed as arthritis, traumatic or nontraumatic, of the sacro-iliac joint, and which were treated by arthrodesis by the method devised by the first author. The cases of tuberculous arthritis in which similar treatments have been given are reported in a separate article which is abstracted elsewhere in this Report of Progress. The diagnosis was based on the history of pain in the region of the sacro-iliac joint and pain radiation in the leg over the area supplied by the first and second sacral nerves (posterior surface of the thigh and outer side of the calf), on the physical examination with demonstration of list of the spine to the opposite side, tenderness over the posterior sacro-iliac ligaments, limitation of movement and production of pain on raising the leg with the knee extended, demonstration of tenderness over the sacro-iliac joint by rectal examination, and on the roentgen-ray examination, which in certain cases showed pubic disalinement or actual arthritic changes in the joint and in others merely a widened joint space. There were twenty-six cases in the group. The operation has been previously described, but briefly consists in exposing the outer surface of the ilium by turning down a muscle flap in the gluteal region and then cutting a window through into the joint. The cartilage is removed and the bone plug which was removed from the ilium is then replaced and driven inward until countersunk in the sacrum. There was no operative mortality. End-results are given in twenty-six cases. Of these, twenty-three patients were completely relieved of pain. Of the three remaining patients, two complained of persistence of pain in the calf of the leg, but stated that this was far less severe than formerly and was decreasing. They have resumed their former occupations in full. The third patient showed a traumatic arthritis of both sacro-iliac joints. One side was operated on and relief of pain resulted, but there was still local and radiation pain present on the other side. Seven of the twenty-six cases have shown a stiffness in either the calf or hamstring muscles or both for varying periods of from two to six months after operation.

27. Smith-Petersen, M. N., and Rogers, William: J. Bone & Joint Surg. 8:118 (Jan.) 1926.

Two of the twenty-six cases are reported as failures and two as partial failures.

[ED. NOTE.—The authors of this article are to be congratulated on the thoroughness of their study and the critical attitude that they have maintained. The Smith-Petersen operation represents a distinct advance over other methods of securing ankylosis of the sacro-iliac joint, and the high percentage of successful results reported by the authors speaks for the care with which they have selected their cases. For others, however, a word of caution is necessary. The indications for operation in cases of so-called sacro-iliac strain or relaxation are by no means clear, nor even among the orthopedic surgeons is there unanimity of opinion as to what constitutes the sacro-iliac syndrome. Ill advised surgery in cases in which the patient might be made well by properly managed nonoperative treatment or in cases that have been diagnosed erroneously will not advance the cause of orthopedic surgery and only tends to cast discredit on the operation. Until more definite knowledge has been obtained on these points the operation should be employed with discretion only in carefully studied and controlled cases, and the end-results should be compiled and reported. It is important to point out that the cases here reported were all chronic cases.]

Lack of Functional Gain Following Osteotomy of the Hip.—Chlumsky [28] has noticed that in certain cases of old hip joint disease with ankylosis in positions of deformity, functional improvement following osteotomy to correct the deformity frequently does not take place; in fact, the gait may be worse than before the operation. This is due, according to Chlumsky, to the adaptation to the deformity which the body has undergone during the years when it was present. Relaxation of the ligaments of the knee and genu valgum is an example of such a process. After correction of the position of the hip the instability of the knee now becomes apparent, whereas before it caused no trouble. Static scoliosis with sinking of the pelvis is another factor. Long standing deformities in elderly people should therefore be approached with caution.

The Rôle of the Tensor Fasciae Femoris in Producing Deformity.—Yount [29] believes that the tensor fasciae femoris plays an important part in the production of deformities of the leg. Its contraction causes permanent flexion of the hip and by its pull through the iliotibial band it leads to knee flexion, knock-knee, and outward rotation of the lower leg. Subcutaneous fasciotomy of the iliotibial band has in his hands been of marked benefit in securing simultaneous correction of the hip flexion and

28. Chlumsky, V.: Zentralbl. f. Chir. **52**:2298 (Oct. 10) 1925.

29. Yount, C. C.: J. Bone & Joint Surg. **8**:171 (Jan.) 1926.

knock-knee. The knee should be kept completely extended during the correction of a flexion deformity of the hip. Simple subcutaneous fasciotomy is considered advisable even in mild degrees of deformity in cases in which all three deformities are present, as the time required for complete correction is materially shortened. In children above the age of 6 years, when all three deformities are present a more radical procedure is advised. The iliotibial band should be completely divided and in addition the fascia should be cut laterally as far as the biceps tendon and mesially to the middle of the anterior surface of the thigh.

Traumatic Chondropathy of the Patella.—Traumatic chondropathy is a term that Fruend [30] applies to a condition of localized ostearthritis of the patella which he has observed in seven cases. He recognizes three stages of the process. In the first there is a localized elevation of a small portion of the cartilage on the posterior surface of the patella. The surface is intact, but the cartilage feels soft and elastic. In the second stage the cartilage is lacerated in several longitudinal fissures. This is followed by a gradual necrosis of the cartilage until in the third stage the subchondral bone lies bare and is rough and hard. From this stage the process goes on to a general ostearthritic change of the entire joint. The typical diagnostic sign is the production of pain by pressing the patella against the femur when the knee is flexed, although this sign is absent when the knee is extended. In the latter position the pain may be elicited by moving the patella firmly over the lateral condyle. The treatment consists in excision of the necrotic area. In some cases the opposing surface of the trochlea is likewise affected and must also be excised. Complete recovery was obtained in all cases after operation.

[ED. NOTE.—Some of us have encountered this condition as part of a generalized ostearthritic involvement of the knee, but we would be cautious in regarding it as an entity or in expecting any marked improvement from operation.]

Calcaneal Spurs.—Lewin [31] emphasizes the fact that calcaneal spurs are not necessarily of gonorrheal origin. Other organisms, metabolic disturbances, trauma and foot strain may produce similar results. Painful heels and the demonstration of spurs on roentgen-ray examination make the diagnosis clear. The prognosis is stated to be good unless there is an arthritis present. He warns against the removal of the spurs unless this can be done with little operative trauma. The size of the spur has no relation to the amount of trouble it may cause.

[ED. NOTE.—We do not agree with Lewin in regarding the spur as the cause and the painful heel as the effect. We have seen many

30. Fruend, H.: Zentralbl. f. Chir. **53**:707 (March 20) 1926.

31. Lewin, Philip: Calcaneal Spurs, Arch. Surg. **12**:117 (Jan.) 1926.

cases in which the spur had undoubtedly been present for years before the symptoms were noted. We regard most of these spurs as osteophytic manifestations of a chronic arthritis similar in every way to the lipping at the margins of joints. The pain is the result of an active inflammatory process, often a bursitis, and with rest and protection will disappear even though the spur persists. Relief following operation in many cases is to be ascribed more to the enforced rest than to the removal of the spur.]

(To be continued)